CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: 074821

Trade Name : TRIAMTERENE AND HYDROCHLORTHIAZIDE CAPSULES USP 37.5MG/25MG

Generic Name: Triamterene and Hydrochlorthiazide Capsules USP 37.5mg/25mg

Sponsor : Geneva Pharmaceuticals, Inc.

Approval Date: June 5, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074821

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074821

APPROVAL LETTERS

ANDA 74-821

JUN 5 1997

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Dear Madam:

This is in reference to your abbreviated new drug application dated December 29, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Triamterene and Hydrochlorothiazide Capsules USP, 37.5 mg/25 mg.

Reference is also made to your amendments dated May 6, August 9 and November 27, 1996; and March 28, April 8, and May 8, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Triamterene and Hydrochlorothiazide Capsules USP, 37.5 mg/25 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug [Dyazide® Capsules of SmithKline Beecham Pharmaceuticals]. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours.

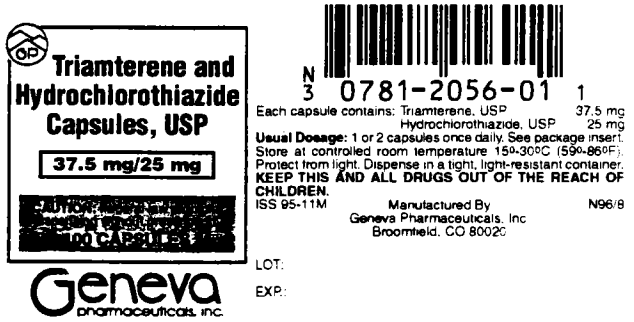
6/5/97

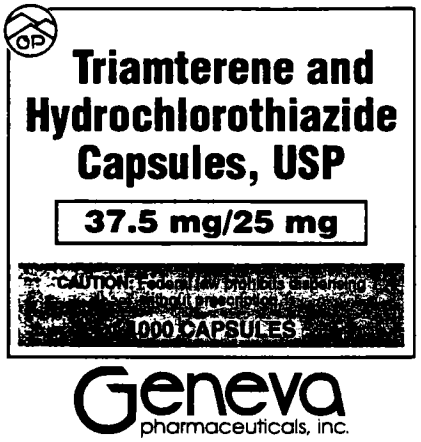
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074821

FINAL PRINTED LABELING





N 3 0781-2056-10 3

Each capsule contains: Triamterene, USP 37.5 mg
Hydrochlorothiazide, USP 25 mg

Usual Dosage: 1 or 2 capsules once daily. See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
Dispense in a tight, light-resistant container.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
ISS 95-11M N96/8

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP.:

7188

TRIAMTERENE AND HYDROCHLOROTHIAZIDE CAPSULES, USP

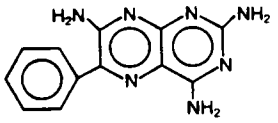
7188-4

JUN 5 1997

DESCRIPTION: Triamterene is an antikaluretic agent and hydrochlorothiazide is a diuretic/antihypertensive agent.

At 50°C, triamterene is practically insoluble in water (less than 0.1%). It is soluble in formic acid, sparingly soluble in methoxyethanol, and very slightly soluble in alcohol.

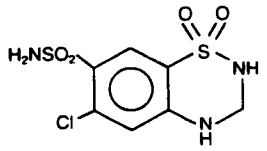
Triamterene is 2,4,7-triamino-6-phenylpteridine with a chemical formula of $C_{12}H_{11}N_7$ and a molecular weight of 253.27. The structural formula for triamterene is



TRIAMTERENE

Hydrochlorothiazide is slightly soluble in water. It is soluble in dilute ammonia, dilute aqueous sodium hydroxide, and dimethylformamide. It is sparingly soluble in methanol.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2, 4-benzothiadiazine-7-sulfonamide 1,1-dioxide with a chemical formula of $C_7H_8ClN_3O_4S_2$ and a molecular weight of 297.75. The structural formula for hydrochlorothiazide is:



HYDROCHLOROTHIAZIDE

Each capsule, for oral administration, contains 37.5 mg triamterene and 25 mg hydrochlorothiazide. Inactive ingredients include: citric acid, glycine, anhydrous lactose, magnesium stearate, Polysorbate 80, povidone, and sodium starch glycolate. The capsule shells and imprinting inks contain: D & C Yellow #10 Aluminum Lake, FD & C Blue #1 Aluminum Lake, FD & C Blue #2 Aluminum Lake, FD & C Red #40 Aluminum Lake, gelatin, pharmaceutical glaze, propylene glycol, synthetic black iron oxide, and titanium dioxide.

This product complies with dissolution test #3.

CLINICAL PHARMACOLOGY: Triamterene and hydrochlorothiazide is a diuretic/antihypertensive drug product that combines natriuretic and antikaluretic effects. Each component complements the action of the other.

The triamterene component of triamterene and hydrochlorothiazide capsule exerts its diuretic effect on the distal renal tubule to inhibit the reabsorption of sodium in exchange for potassium and hydrogen ions. Its natriuretic activity is limited by the amount of sodium reaching its site of action. Although it blocks the increase in this exchange that is stimulated by mineralocorticoids (chiefly aldosterone) it is not a competitive antagonist of aldosterone and its activity can be demonstrated in adrenalectomized rats and patients with Addison's disease. As a result, the dose of triamterene required is not proportionally related to the level of mineralocorticoid activity, but is dictated by the response of the individual patients, and the kaluretic effect of concomitantly administered drugs. By inhibiting the distal tubular exchange mechanism, triamterene maintains or increases the sodium excretion and reduces the excess loss of potassium, hydrogen, and chloride ions induced by hydrochlorothiazide. As with hydrochlorothiazide, triamterene may reduce glomerular filtration and renal plasma flow. Via this mechanism it may reduce uric acid excretion, although it has no tubular effect on uric acid reabsorption or secretion. Triamterene does not affect calcium excretion. No predictable antihypertensive effect has been demonstrated for triamterene.

The hydrochlorothiazide component blocks the reabsorption of sodium and chloride ions, and thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted. A portion of the additional sodium presented to the distal tubule is exchanged there for potassium and hydrogen ions. With continued use of hydrochlorothiazide and depletion of sodium, compensatory mechanisms tend to increase this exchange and may produce excessive loss of potassium, hydrogen and chloride ions. Hydrochlorothiazide also decreases the excretion of calcium and uric acid, may increase the excretion of iodide and may reduce glomerular filtration rate. The exact mechanism of the antihypertensive effect of hydrochlorothiazide is not known.

Duration of diuretic activity and effective dosage range of the hydrochlorothiazide and triamterene components are similar. Onset of diuresis with triamterene and hydrochlorothiazide takes place within one hour, peaks at two to three hours and tapers off during the subsequent seven to nine hours.

Triamterene and hydrochlorothiazide capsule are well absorbed.

It has been reported that upon administration of a single oral dose to fasted normal male volunteers, the following mean pharmacokinetic parameters were determined:

	AUC(0-48) ng*hrs/mL (± SD)	Cmax ng/mL (± SD)	Median Tmax hrs	Ae mg (± SD)
triamterene	148.7 (87.9)	46.4 (29.4)	1.1	2.7 (1.4)
hydroxytriamterene sulfate	1865 (471)	720 (364)	1.3	19.7 (6.1)
hydrochlorothiazide	834 (177)	135.1 (35.7)	2.0	14.3 (3.8)

where AUC(0-48), Cmax, Tmax and Ae represent area under the plasma concentration versus time plot, maximum plasma concentration, time to

hydrochlorothiazide is not known.

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where AUC(0–48), Cmax, Tmax and Ae represent area under the plasma concentration versus time plot, maximum plasma concentration, time to reach Cmax and amount excreted in urine over 48 hours.

One triamterene and hydrochlorothiazide capsule is bioequivalent to a single-entity 25 mg hydrochlorothiazide tablet and 37.5 mg triamterene capsule used in the double-blind clinical trial below. (See Clinical Trials.)

In a limited study involving 12 subjects, coadministration of a marketed brand of triamterene and hydrochlorothiazide capsule with a high-fat meal resulted in: (1) an increase in the mean bioavailability of triamterene by about 67% (90% confidence interval = 0.99, 1.90), p-hydroxytriamterene sulfate by about 50% (90% confidence interval = 1.06, 1.77), hydrochlorothiazide by about 17% (90% confidence interval = 0.90, 1.34); (2) increases in the peak concentrations of triamterene and p-hydroxytriamterene; and (3) a delay of up to 2 hours in the absorption of the active constituents.

Clinical Trials: A placebo-controlled, double-blind trial was conducted to evaluate the efficacy of triamterene and hydrochlorothiazide capsules. This trial demonstrated that triamterene and hydrochlorothiazide capsules 37.5 mg/25 mg were effective in controlling blood pressure while reducing the incidence of hydrochlorothiazide-induced hypokalemia. This trial involved 636 patients with mild to moderate hypertension controlled by hydrochlorothiazide 25 mg daily and who had hypokalemia (serum potassium <3.5 mEq/L) secondary to the hydrochlorothiazide. Patients were randomly assigned to 4 weeks' treatment with once-daily regimens of 25 mg hydrochlorothiazide plus placebo, or 25 mg hydrochlorothiazide combined with one of the following doses of triamterene: 25 mg, 37.5 mg, 50 mg or 75 mg.

Blood pressure and serum potassium were monitored at baseline and throughout the trial. All five treatment groups had similar mean blood pressure and serum potassium concentrations at baseline (mean systolic blood pressure range: 137±14 mmHg to 140±16 mmHg; mean diastolic blood pressure range: 86±9 mmHg to 88±8 mmHg; mean serum potassium range: 2.3 to 3.4 mEq/L with the majority of patients having values between 3.1 and 3.4 mEq/L).

While all triamterene regimens reversed hypokalemia, at week 4 the 37.5 mg regimen proved optimal compared with the other tested regimens. On this regimen, 81% of the patients had a significant ($p<0.05$) reversal of hypokalemia vs. 59% of patients on the placebo/hydrochlorothiazide regimen. The mean serum potassium concentration on 37.5 mg triamterene went from 3.2±0.2 mEq/L at baseline to 3.7±0.3 mEq/L at week 4, a significantly greater ($p<0.05$) improvement than that achieved with placebo/hydrochlorothiazide (i.e., 3.2±0.2 mEq/L at baseline and 3.5±0.4 mEq/L at week 4). Also, 51% of patients in the 37.5 mg triamterene group had an increase in serum potassium of ≥0.5 mEq/L at week 4 vs. 33% in the placebo group. The 37.5 mg triamterene/25 mg hydrochlorothiazide regimen also maintained control of blood pressure: mean supine systolic blood pressure at week 4 was 138±21 mmHg while mean supine diastolic blood pressure was 87±13 mmHg.

INDICATIONS AND USAGE: This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

Triamterene and hydrochlorothiazide capsules are indicated for the treatment of hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone.

Triamterene and hydrochlorothiazide capsules are also indicated for those patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked.

Triamterene and hydrochlorothiazide may be used alone or as an adjunct to other antihypertensive drugs, such as beta-blockers. Since triamterene and hydrochlorothiazide may enhance the action of these agents, dosage adjustments may be necessary.

Usage in Pregnancy: The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy, and there is no satisfactory evidence that they are useful in the treatment of developed toxemia.

Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy. Diuretics are indicated in pregnancy when edema is due to pathologic causes, just as they are in the absence of pregnancy. Dependent edema in pregnancy, resulting from restriction of venous return by the expanded uterus, is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is illogical and unnecessary. There is hypervolemia during normal pregnancy which is harmful to neither the fetus nor the mother (in the absence of cardiovascular disease), but which is associated with edema, including generalized edema, in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances, this edema may cause extreme discomfort which is not relieved by rest. In these cases, a short course of diuretics may provide relief and may be appropriate.

CONTRAINDICATIONS:

Antikaliuretic Therapy and Potassium Supplementation: Triamterene and hydrochlorothiazide should not be given to patients receiving other potassium-sparing agents such as spironolactone, amiloride or other formulations containing triamterene. Concomitant potassium-containing salt substitutes should also not be used.

Potassium supplementation should not be used with triamterene and hydrochlorothiazide except in severe cases of hypokalemia. Such concomitant therapy can be associated with rapid increases in serum potassium levels. If potassium supplementation is used, careful monitoring of the serum potassium level is necessary.

Impaired Renal Function: Triamterene and hydrochlorothiazide is contraindicated in patients with anuria, acute and chronic renal insufficiency or significant renal impairment.

Hypersensitivity: Hypersensitivity to either drug in the preparation or to other sulfonamide-derived drugs is a contraindication.

Hyperkalemia: Triamterene and hydrochlorothiazide should not be used in patients with preexisting elevated serum potassium.

WARNINGS: Hyperkalemia

Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium-sparing diuretic combinations, including triamterene and hydrochlorothiazide. Hyperkalemia is more likely to occur in patients with renal impairment and diabetes (even without evidence of renal impairment), and in the elderly or severely ill. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving triamterene and hydrochlorothiazide, when dosages are changed or with any illness that may influence renal function.

If hyperkalemia is suspected (warning signs include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia and shock), an electrocardiogram (ECG) should be obtained. However, it is important to monitor serum potassium levels because hyperkalemia may not be associated with ECG changes.

If hyperkalemia is present, triamterene and hydrochlorothiazide should be discontinued immediately and a thiazide alone should be substituted. If the serum potassium exceeds 6.5 mEq/liter, more vigorous therapy is required. The clinical situation dictates the procedures to be employed. These include the intravenous administration of calcium chloride injection, sodium bicarbonate injection and/or the oral or parenteral administration of glucose with a rapid-acting insulin preparation. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis.

The development of hyperkalemia associated with potassium-sparing diuretics is accentuated in the presence of renal impairment (see CONTRAINDICATIONS section). Patients with mild renal functional impairment should not receive this drug without frequent and continuing monitoring of serum electrolytes. Cumulative drug effects may be observed in patients with impaired renal function. The renal clearances of hydrochlorothiazide and the

amterene went from 3.2±0.2 mEq/L at baseline to 3.7±0.3 mEq/L at week 4, a significantly greater ($p<0.05$) improvement than that achieved with placebo/hydrochlorothiazide (i.e., 3.2±0.2 mEq/L at baseline and 3.5±0.4 mEq/L at week 4). Also, 51% of patients in the 37.5 mg triamterene group had an increase in serum potassium of ≥0.5 mEq/L at week 4 vs. 33% in the placebo group. The 37.5 mg triamterene/25 mg hydrochlorothiazide regimen also maintained control of blood pressure: mean supine systolic blood pressure at week 4 was 138±21 mmHg while mean supine diastolic blood pressure was 87±13 mmHg.

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Triamterene and hydrochlorothiazide capsules are also indicated for those patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked.

Triamterene and hydrochlorothiazide may be used alone or as an adjunct to other antihypertensive drugs, such as beta-blockers. Since triamterene and hydrochlorothiazide may enhance the action of these agents, dosage adjustments may be necessary.

Usage In Pregnancy: The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy, and there is no satisfactory evidence that they are useful in the treatment of developed toxemia.

Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy. Diuretics are indicated in pregnancy when edema is due to pathologic causes, just as they are in the absence of pregnancy. Dependent edema in pregnancy, resulting from restriction of venous return by the expanded uterus, is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is illogical and unnecessary. There is hypervolemia during normal pregnancy which is harmful to neither the fetus nor the mother (in the absence of cardiovascular disease), but which is associated with edema, including generalized edema, in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances, this edema may cause extreme discomfort which is not relieved by rest. In these cases, a short course of diuretics may provide relief and may be appropriate.

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If hyperkalemia is suspected (warning signs include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia and shock), an electrocardiogram (ECG) should be obtained. However, it is important to monitor serum potassium levels because hyperkalemia may not be associated with ECG changes.

If hyperkalemia is present, triamterene and hydrochlorothiazide should be discontinued immediately and a thiazide alone should be substituted. If the serum potassium exceeds 6.5 mEq/liter, more vigorous therapy is required. The clinical situation dictates the procedures to be employed. These include the intravenous administration of calcium chloride injection, sodium bicarbonate injection and/or the oral or parenteral administration of glucose with a rapid-acting insulin preparation. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis.

The development of hyperkalemia associated with potassium-sparing diuretics is accentuated in the presence of renal impairment (see CONTRAINDICATIONS section). Patients with mild renal functional impairment should not receive this drug without frequent and continuing monitoring of serum electrolytes. Cumulative drug effects may be observed in patients with impaired renal function. The renal clearances of hydrochlorothiazide and the pharmacologically active metabolite of triamterene, the sulfate ester of hydroxytriamterene, have been shown to be reduced and the plasma levels increased following triamterene and hydrochlorothiazide administration to elderly patients and patients with impaired renal function.

Hyperkalemia has been reported in diabetic patients with the use of potassium-sparing agents even in the absence of apparent renal impairment. Accordingly, serum electrolytes must be frequently monitored if triamterene and hydrochlorothiazide is used in diabetic patients.

Metabolic or Respiratory Acidosis: Potassium-sparing therapy should also be avoided in severely ill patients in whom respiratory or metabolic acidosis may occur. Acidosis may be associated with rapid elevations in serum potassium levels. If triamterene and hydrochlorothiazide is employed, frequent evaluations of acid/base balance and serum electrolytes are necessary.

PRECAUTIONS:

Impaired Hepatic Function: Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate hepatic coma in patients with severe liver disease. Potassium depletion induced by the thiazide may be important in this connection. Administer triamterene and hydrochlorothiazide cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor. If mental confusion increases, discontinue triamterene and hydrochlorothiazide for a few days. Attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion.

Hypokalemia: Hypokalemia is uncommon with triamterene and hydrochlorothiazide but, should it develop, corrective measures should be taken such as potassium supplementation or increased intake of potassium-rich foods. Institute such measures cautiously with frequent determinations of serum potassium levels, especially in patients receiving digitalis or with a history of cardiac arrhythmias. If serious hypokalemia (serum potassium less than 3.0 mEq/L) is demonstrated by repeat serum potassium determinations, triamterene and hydrochlorothiazide should be discontinued and potassium chloride supplementation initiated. Less serious hypokalemia should be evaluated with regard to other coexisting conditions and treated accordingly.

Electrolyte Imbalance: Electrolyte imbalance, often encountered in such conditions as heart failure, renal disease or cirrhosis of the liver, may also be aggravated by diuretics and should be considered during triamterene and hydrochlorothiazide therapy when using high doses for prolonged periods or in patients on a salt-restricted diet. Serum determinations of electrolytes should be performed, and are particularly important if the patient is vomiting excessively or receiving fluids parenterally. Possible fluid and electrolyte imbalance may be indicated by such warning signs as: dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal symptoms.

Hypochloremia: Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Renal Stones: Triamterene has been found in renal stones in association with the other usual calculus components. Triamterene and hydrochlorothiazide should be used with caution in patients with a history of renal stones.

Laboratory Tests:

Serum Potassium: The normal adult range of serum potassium is 3.5 to 5.0 mEq per liter with 4.5 mEq often being used for a reference point. If hypokalemia should develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods.

Institute such measures cautiously with frequent determinations of serum potassium levels. Potassium levels persistently above 6 mEq per liter require careful observation and treatment. Serum potassium levels do not necessarily indicate true body potassium concentration. A rise in plasma pH may cause a decrease in plasma potassium concentration and an increase in the intracellular potassium concentration. Discontinue corrective measures for hypokalemia immediately if laboratory determinations reveal an abnormal elevation of serum potassium. Discontinue triamterene and hydrochlorothiazide and substitute a thiazide diuretic alone until potassium levels return to normal.

Serum Creatinine and BUN: Triamterene and hydrochlorothiazide may produce an elevated blood urea nitrogen level, creatinine level or both. This apparently is secondary to a reversible reduction of glomerular filtration rate or a depletion of intravascular fluid volume (prerenal azotemia) rather than renal toxicity; levels usually return to normal when triamterene and hydrochlorothiazide is discontinued. If azotemia increases, discontinue triamterene and hydrochlorothiazide. Periodic BUN or serum creatinine determinations should be made, especially in elderly patients and in patients with suspected or confirmed renal insufficiency.

Serum PBI: Thiazide may decrease serum PBI levels without sign of thyroid disturbance.

Parathyroid Function: Thiazides should be discontinued before carrying out tests for parathyroid function. Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as bone resorption and peptic ulceration have not been seen.

Drug Interactions:

Angiotensin-converting enzyme inhibitors: Potassium-sparing agents should be used with caution in conjunction with angiotensin-converting enzyme (ACE) inhibitors due to an increased risk of hyperkalemia.

Oral hypoglycemic drugs: Concurrent use with chlorpropamide may increase the risk of severe hyponatremia.

Nonsteroidal anti-inflammatory drugs: A possible interaction resulting in acute renal failure has been reported in a few patients on triamterene and hydrochlorothiazide when treated with indomethacin, a nonsteroidal anti-inflammatory agent. Caution is advised in administering nonsteroidal anti-inflammatory agents with triamterene and hydrochlorothiazide.

Lithium: Lithium generally should not be given with diuretics because they reduce its renal clearance and increase the risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy with triamterene and hydrochlorothiazide.

Surgical considerations: Thiazides have been shown to decrease arterial responsiveness to norepinephrine (an effect attributed to loss of sodium). This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine (an effect attributed to potassium loss); consequently caution should be observed in patients undergoing surgery.

Other Considerations: Concurrent use of hydrochlorothiazide with amphotericin B or corticosteroids or corticotropin (ACTH) may intensify electrolyte imbalance, particularly hypokalemia, although the presence of triamterene minimizes the hypokalemic effect.

Thiazides may add to or potentiate the action of other antihypertensive drugs. See INDICATIONS AND USAGE for concomitant use with other antihypertensive drugs.

The effect of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary.

Triamterene and hydrochlorothiazide may raise the level of blood uric acid; dosage adjustments of antigout medication may be necessary to control hyperuricemia and gout.

The following agents given together with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia because of the potassium-sparing nature of triamterene, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq per liter of whole blood when stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium); salt substitutes (most contain substantial amounts of potassium).

Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium levels by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake.

Chronic or overuse of laxatives may reduce serum potassium levels by promoting excessive potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene.

The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine.

Drug/Laboratory Test Interactions: Triamterene and quinidine have similar fluorescence spectra; thus, triamterene and hydrochlorothiazide will interfere with the fluorescent measurement of quinidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Long-term studies have not been conducted with the triamterene and hydrochlorothiazide combination, or with triamterene alone.

Hydrochlorothiazide: Two-year feeding studies in mice and rats, conducted under the auspices of the National Toxicology Program (NTP), treated mice and rats with doses of hydrochlorothiazide up to 600 and 100 mg/kg/day, respectively. On a body-weight basis, these doses are 600 times (in mice) and 100 times (in rats) the Maximum Recommended Human Dose (MRHD) for the hydrochlorothiazide component of triamterene and hydrochlorothiazide capsules at 50 mg/day (or 1 mg/kg/day based on 50 kg individuals). On the basis of body-surface area, these doses are 56 times (in mice) and 21 times (in rats) the MRHD. These studies uncovered no evidence of carcinogenic potential of hydrochlorothiazide in rats or female mice, but there was equivocal evidence of hepatocarcinogenicity in male mice.

Mutagenesis: Studies of the mutagenic potential of the triamterene and hydrochlorothiazide combination, or of triamterene alone have not been performed.

Hydrochlorothiazide: Hydrochlorothiazide was not genotoxic in *in vitro* assays using strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 of *Salmonella typhimurium* (the Ames test); in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations; or in *in vivo* assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) test, and in the mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide of 43 to 1300 mcg/mL. Positive test results were also obtained in the *Aspergillus nidulans* nondisjunction assay, using an unspecified concentration of hydrochlorothiazide.

Impairment of Fertility: Studies of the effects of the triamterene and hydrochlorothiazide combination, or of triamterene alone on animal reproductive function have not been conducted.

Hydrochlorothiazide: Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg/day, respectively, prior to mating and throughout gestation. Corresponding multiples of the MRHD are 100 (mice) and 4 (rats) on the basis of body-weight and 9.4 (mice) and 0.8 (rats) on the basis of body-surface area.

Pregnancy: *Category C: Teratogenic Effects*

Triamterene and Hydrochlorothiazide: Animal reproduction studies to determine the potential for fetal harm by triamterene and hydrochlorothiazide have not been conducted. However, a One Generation Study in the rat approximated triamterene and hydrochlorothiazide composition by using a 1:1 ratio of triamterene to hydrochlorothiazide (30:30 mg/kg/day); there was no evidence of teratogenicity at those doses which were, on a body-weight basis, 15 and 30 times, respectively, the MRHD, and on the basis of body-surface area, 3.1 and 6.2 times, respectively, the MRHD.

The safe use of triamterene and hydrochlorothiazide in pregnancy has not been established since there are no adequate and well-controlled studies with triamterene and hydrochlorothiazide in pregnant women. Triamterene and hydrochlorothiazide should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Triamterene: Reproduction studies have been performed in rats at doses as high as 20 times the MRHD on the basis of body-weight, and 6 times the human dose on the basis of body-surface area without evidence of harm to the fetus due to triamterene.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Hydrochlorothiazide: Hydrochlorothiazide was orally administered to pregnant mice and rats during respective periods of major organogenesis

Mutagenesis: Studies of the mutagenic potential of the triamterene and hydrochlorothiazide combination, or of triamterene alone have not been performed.

Hydrochlorothiazide: Hydrochlorothiazide was not genotoxic in *in vitro* assays using strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 of *Salmonella typhimurium* (the Ames test); in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations; or in *in vivo* assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) test, and in the mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide of 43 to 1300 mcg/mL. Positive test results were also obtained in the *Aspergillus nidulans* nondisjunction assay, using an unspecified concentration of hydrochlorothiazide.

Impairment of Fertility: Studies of the effects of the triamterene and hydrochlorothiazide combination, or of triamterene alone on animal reproductive function have not been conducted.

Hydrochlorothiazide: Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg/day, respectively, prior to mating and throughout gestation. Corresponding multiples of the MRHD are 100 (mice) and 4 (rats) on the basis of body-weight and 9.4 (mice) and 0.8 (rats) on the basis of body-surface area.

Pregnancy: ***Category C:*** *Teratogenic Effects:*

Triamterene and Hydrochlorothiazide: Animal reproduction studies to determine the potential for fetal harm by triamterene and hydrochlorothiazide have not been conducted. However, a One Generation Study in the rat approximated triamterene and hydrochlorothiazide composition by using a 1:1 ratio of triamterene to hydrochlorothiazide (30:30 mg/kg/day); there was no evidence of teratogenicity at those doses which were, on a body-weight basis, 15 and 30 times, respectively, the MRHD, and on the basis of body-surface area, 3.1 and 6.2 times, respectively, the MRHD.

The safe use of triamterene and hydrochlorothiazide in pregnancy has not been established since there are no adequate and well-controlled studies with triamterene and hydrochlorothiazide in pregnant women. Triamterene and hydrochlorothiazide should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Triamterene: Reproduction studies have been performed in rats at doses as high as 20 times the MRHD on the basis of body-weight, and 6 times the human dose on the basis of body-surface area without evidence of harm to the fetus due to triamterene.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Hydrochlorothiazide: Hydrochlorothiazide was orally administered to pregnant mice and rats during respective periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively. At these doses, which are multiples of the MRHD equal to 3000 for mice and 1000 for rats, based on body-weight, and equal to 282 for mice and 206 for rats, based on body-surface area, there was no evidence of harm to the fetus.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: Thiazides and triamterene have been shown to cross the placental barrier and appear in cord blood. The use of thiazides and triamterene in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, pancreatitis, thrombocytopenia and possible other adverse reactions which have occurred in the adult.

Nursing Mothers: Thiazides and triamterene in combination have not been studied in nursing mothers. Triamterene appears in animal milk; this may occur in humans. Thiazides are excreted in human breast milk. If use of the combination drug product is deemed essential, the patient should stop nursing.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: Adverse effects are listed in decreasing order of frequency; however, the most serious adverse effects are listed first regardless of frequency. The serious adverse effects associated with triamterene and hydrochlorothiazide capsules have commonly occurred in less than 0.1% of patients treated with this product.

Hypersensitivity: anaphylaxis, rash, urticaria, photosensitivity.

Cardiovascular: arrhythmia, postural hypotension.

Metabolic: diabetes mellitus, hyperkalemia, hyperglycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia.

Gastrointestinal: jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain.

Renal: acute renal failure (one case of irreversible renal failure has been reported), interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment.

Hematologic: leukopenia, thrombocytopenia and purpura, megaloblastic anemia.

Musculoskeletal: muscle cramps.

Central Nervous System: weakness, fatigue, dizziness, headache, dry mouth.

Miscellaneous: impotence, sialadenitis.

Thiazides alone have been shown to cause the following additional adverse reactions:

Central Nervous System: paresthesias, vertigo.

Ophthalmic: xanthopsia, transient blurred vision.

Respiratory: allergic pneumonitis, pulmonary edema, respiratory distress.

Other: necrotizing vasculitis, exacerbation of lupus.

Hematologic: aplastic anemia, agranulocytosis, hemolytic anemia.

Neonate and Infancy: thrombocytopenia and pancreatitis – rarely, in newborns whose mothers have received thiazides during pregnancy.

OVERDOSAGE: Electrolyte imbalance is the major concern (See WARNINGS section). Symptoms reported include: polyuria, nausea, vomiting, weakness, lassitude, fever, flushed face and hyperactive deep tendon reflexes. If hypotension occurs, it may be treated with pressor agents such as norepinephrine to maintain blood pressure. Carefully evaluate the electrolyte pattern and fluid balance. Induce immediate evacuation of the stomach through emeses or gastric lavage. There is no specific antidote.

Reversible acute renal failure following ingestion of 50 tablets of a product containing a combination of 50 mg triamterene and 25 mg hydrochlorothiazide has been reported.

Although triamterene is largely protein-bound (approximately 67%), there may be some benefit to dialysis in cases of overdosage.

DOSAGE AND ADMINISTRATION: The usual dose of triamterene and hydrochlorothiazide capsules 37.5 mg/25 mg is one or two capsules given once daily, with appropriate monitoring of serum potassium and of the clinical effect. (See WARNINGS, Hyperkalemia.)

HOW SUPPLIED: Capsules containing 37.5 mg triamterene and 25 mg hydrochlorothiazide are available for oral administration as white capsules imprinted GG 606 in black ink in bottles of 100 and 1000.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from light.

Dispense in a tight, light-resistant container.

Caution: Federal law prohibits dispensing without prescription.

Rev. 97-3M

7188-4 C9714

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074821

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-821

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2655 W.Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

4. LEGAL BASIS FOR SUBMISSION
Based on the approved listed drug Dyazide® Capsules (Smithkline Beecham) containing 25/37.5 mg HCTZ and Triamterene.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME
Triamterene and HCTZ USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FDA: 2/28/97 NA/Fax letter issued.

Firm:	12/29/95	Original submission
	11/27/96	Corr.(Bio issue)
	3/28/97	Response to NA/Fax letter dated 2/28/97.
	4/7/97	Tel. Amendment

10. PHARMACOLOGICAL CATEGORY
Diuretic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsules

14. POTENCY
37.5/25 mg

16. RECORDS AND REPORTS N/A

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER:
J.Fan

DATE COMPLETED:
4/14/97

cc: ANDA 74-821
DUP Jacket
Division File

Endorsements:

HFD-623/J.Fan/ 4/14/97, 4/15/97
HFD-623/V.Sayeed/
x:\new\firmsam\geneva\ltrs&rev\74821n3.d
F/T by:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074821

BIOEQUIVALENCE REVIEW(S)

DN

ANDA 74-821

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
Broomfield CO 80038-0446

MAY 2 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Triamterene and Hydrochlorothiazide Capsules USP 37.5/25 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APR 30 1997 2 iV

Triamterene/Hydrochlorothiazide
37.5 mg/25 mg Capsule
ANDA # **74-821**
Reviewer: Z.Z. Wahba
File #74821a.n96

Geneva Pharmaceuticals
Broomfield, CO
Submission Date:
November 27, 1996

AMENDMENT TO A REVIEWED IN VIVO BIOEQUIVALENCE STUDY AND DISSOLUTION DATA (Dated July 18, 1996)

BACKGROUND

The firm has previously submitted an in vivo bioequivalence study (single dose) under fasting and non-fasting conditions comparing its Triamterene/Hydrochlorothiazide Capsules, 37.5 mg/25 mg to the reference listed drug SmithKline Beecham's Dyazide® Capsules, 37.5 mg/25.

The submission was reviewed and was found incomplete by the Division of Bioequivalence (review dated July 18, 1996, ANDA #74-821) due to a deficiency comment regarding the dissolution data. The firm submitted dissolution data using the dissolution medium 0.1N HCl, whereas the USP methodology specifies that the medium should be 0.1 M acetic acid containing 1% polysorbate 20.

Therefore, a new dissolution data using dissolution medium 0.1 M acetic acid containing 1% polysorbate 20 was requested (the communication was dated July 23, 1996).

The USP 23, Supplement #5 (released September 15, 1996) changed its dissolution specification to include three tests.

The firm had previously conducted its dissolution specification according to Test #3 and the met the requirements of the USP dissolution Test #3. The firm should indicate in the drug's labeling that its dissolution meets the USP dissolution requirements of Test #3.

IN VITRO DISSOLUTION TESTING

Method:	USP 23 apparatus 1 (basket) at 100 rpm
Medium:	900 mL of 0.1N HCL
Temperature:	37°C ± 0.5°C
No. Units Tested:	12
Sampling Time:	15, 30, 45 and 60 minutes
Methodology:	
Specification:	NLT (Q) is dissolved in 45 minutes

Test Product: Geneva's triamterene/hydrochlorothiazide capsules 37.5mg/25 mg, lot # 6495058

Reference Product: SmithKline Beecham's Dyazide® capsules 37.5 mg/25 mg, lot #224E50

The dissolution testing results are presented in Table #1.

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Triamterene/Hydrochlorothiazide
Dose Strength: 37.5 mg/25 mg Capsules
ANDA No.:74-821
Firm: Geneva Pharmaceuticals Inc.
Submission Date: December 29, 1995
File Name: 74821sd.d95

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle:X RPM: 100
No. Units Tested: 12 Capsules
Medium:900 mL of 0.1N HCl
Specifications: NLT of the labeled amounts of triamterene and hydrochlorothiazide are dissolved in 45 minutes.
Reference Drug: SmithKline Beecham's Dyazide®
Assay Methodology:

II. Results of In Vitro Dissolution Testing: Triamterene

Sampling Times (min)	Test Product: Triamterene Lot # 6495058 Strength(mg) 37.5			Reference Product: Triamterene Lot # 224E50 Strength(mg) 37.5		
	Mean %	Range	%CV	Mean %	Range	%CV
15	85		4.0	80		6.9
30	95		2.8	93		3.2
45	97		3.0	97		2.5
60	98		2.9	99		1.8

Hydrochlorothiazide

Sampling Times (min)	Test Product: Hydrochlorothiazide Lot # 6495058 Strength(mg) 25			Reference Product: Hydrochlorothiazide Lot # 224E50 Strength(mg) 25		
	Mean %	Range	%CV	Mean %	Range	%CV
15	87		4.1	84		6.1
30	95		3.2	94		2.9
45	97		3.0	96		1.9
60	97		2.9	97		1.8

RECOMMENDATIONS

1. The two in vivo bioequivalence studies conducted by Geneva Pharmaceuticals under fasting and non-fasting conditions on its drug product, Triamterene/Hydrochlorothiazide Capsules, 37.5 mg/25 mg (Lot #6495058), comparing it to the reference listed drug, SmithKline Beecham's Dyazide® capsules, 37.5 mg/25 mg (Lot #224E50) have been found acceptable by the Division of Bioequivalence. The two studies demonstrated that Geneva's Triamterene/Hydrochlorothiazide Capsules, 37.5 mg/25 mg are bioequivalent to the reference listed drug, SmithKline Beecham's Dyazide® capsules, 37.5 mg/25 mg.

2. The dissolution testing data conducted by Geneva Pharmaceuticals on its drug product, Triamterene/Hydrochlorothiazide Capsules, 37.5 mg/25 mg (Lot #6495058) have been found acceptable. The dissolution data met the USP 23 dissolution requirements of Test #3. The firm should indicate in the labeling that its drug dissolution meets the USP dissolution Test #3.

3. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence.

The firm should be informed of the recommendations.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRF

4/24/97

Concur: _____ Date: 4/30/97
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

cc: ANDA 74-821 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Wahba), Drug File, Division File
ZZWahba/041697/042497/file #74821a.n96

ANDA 74-821

JUL 23 1996

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
P.O. BOX 446
Broomfield CO 80038-0446

Dear Madam:

Reference is made to the Abbreviated New Drug Application submitted on December 29, 1995 and the amendment dated May 6, 1996, for Triamterene and Hydrochlorothiazide USP, 37.5 mg/25 mg Capsules.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

> The dissolution data was submitted using the dissolution medium 0.1N HCl, whereas the USP methodology specifies the medium should be 0.1 M acetic acid containing 1% of polysorbate 20. It should be noticed that the Office considers the current USP methodology to be the regulatory method which must be used for dissolution comparison. Therefore, you should resubmit the dissolution data for the test and reference drug products using the current USP methodology. The dissolution testing should be done on capsules from the same lot number that had been used in the *in vivo* bioequivalence study.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUL 18 1996

Triamterene/Hydrochlorothiazide
37.5 mg/25 mg Capsule
ANDA # **74-821**
Reviewer: Z.Z. Wahba
WP 74821s.d95

Geneva Pharmaceuticals
Broomfield, CO
Submission Date:
December 29, 1995

REVIEW OF TWO IN VIVO BIOEQUIVALENCE STUDIES UNDER FASTING CONDITIONS

I. OBJECTIVE:

To review:

1. Geneva's in vivo bioequivalence study (single dose) under fasting and non-fasting conditions comparing its Triamterene/Hydrochlorothiazide Capsules, 37.5 mg/25 mg to the reference listed drug SmithKline Beecham's Dyazide® Capsules, 37.5 mg/25 mg.

2. Dissolution data comparing the test drug product to the reference listed drug.

II. BACKGROUND:

Triamterene/Hydrochlorothiazide is an orally active combination drug which is indicated for the treatment of hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone. Triamterene/Hydrochlorothiazide is a diuretic/antihypertensive drug that combines natriuretic and antikaliuretic effects. Each component complements the action of the other. The hydrochlorothiazide component blocks the reabsorption of sodium and chloride ions, and thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted. The triamterene component inhibits the reabsorption of sodium in exchange for potassium and hydrogen ions.

Hydrochlorothiazide is absorbed from the GI tract. Based on determination of plasma concentrations over a period of at least 24 hours, the plasma half-life of hydrochlorothiazide reportedly ranges from 5.5-14.8 hours. Hydrochlorothiazide is apparently not metabolized and is excreted unchanged in urine. At least 61% of the drug is reportedly eliminated from the body within 24 hours (AHES Drug Information, 1993, p #1611).

Triamterene is rapidly absorbed from the GI tract; however, the degree of absorption varies in different individuals. Peak plasma concentrations of 0.05-0.28 ug/mL are achieved within 2-4 hours following administration of a 100 to 200 mg single oral dose. The plasma half-life of triamterene is 1.5-2.5 hours. The metabolic and excretory fate of triamterene has not been fully determined. The drug is reportedly metabolized to 6-p-hydroxytriamterene which is pharmacologically active and its sulfate conjugate. Triamterene is excreted in urine as unchanged drug and metabolites.

Triamterene/Hydrochlorothiazide is currently marketed as 25mg/37.5mg oral capsules , under the trade name Dyazide® capsules manufactured by SmithKline Beecham.

III. BIOEQUIVALENCE STUDY UNDER FASTING CONDITIONS (clinical study #B-07175)

A. **SPONSOR**:
Geneva Pharmaceuticals, Inc.
2555 West Midway Blvd.
Broomfield, CO 80038-0469

Study site:

Clinical Study Dates:
Period I: Sept. 09-11, 1995
Period II: Sept. 16-18, 1995

B. **STUDY DESIGN**:
Randomized, two-way crossover, single dose study, under fasting conditions.

C. **SUBJECTS**:
Thirty two (32) healthy male subjects were enrolled in the study and all subjects successfully completed the study. The data set used for statistical analyses contained all the data from 32 subjects.

Subject Inclusion Criteria:

1. The subjects were within 18 to 45 years of age, and their body weights were within ± 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.
2. Only medically healthy subjects as determined by normal history, physical examination and laboratory profiles were enrolled in the study.

Subject Exclusion Criteria:

1. History of chronic alcohol consumption or drug addiction.
2. History of cardiovascular, respiratory, renal, gastrointestinal, immunologic, neurologic, hepatic, hematopoietic or psychiatric disease.
3. Tested positive for hepatitis B surface antigen screen or a reactive HIV 1 & 2 antibody screen.
4. Allergy to the class of drug being tested.
5. Use of tobacco in any form
6. Treatment with any known hepatic enzyme inducing or inhibiting agents within the past 30 days prior to dosing.
7. Participated in a previous clinical trail or donated blood within the past 30 days.

Subject Restrictions:

1. No subject took any medications, including OTC products for at least 7 days prior to the beginning of the study and until completion of the study.
2. No alcoholic, xanthine and caffeine containing foods and beverages were allowed for at least 48 hours prior to beginning of the study as well as during the study.

D. **TREATMENT**:

Test Product: 1 x 37.5 mg/25 mg Geneva's Triamterene/ Hydrochlorothiazide capsules, lot # 6495058, lot size capsules, potency 94.9% and 96.4%, content uniformity 95.8% (CV=3.3%) and 95.3% (CV=3.0%), for triamterene and hydrochlorothiazide, respectively.

Reference Product: 1 x 37.5 mg/25 mg SmithKline Beecham's Dyazide® capsules 37.5 mg/25 mg, lot #224E50, potency 96.4% and 100%, content uniformity 99.8% (CV=1.8%) and 95.2% (CV=3.5%), for triamterene and hydrochlorothiazide, respectively. The expiration date: 6/96.

Washout period: 7 days

E. **DRUG, FOOD AND FLUID INTAKE**:

Subjects fasted for at least 10 hours (overnight) before dosing and for 4 hours after dosing. Each dose was followed by 240 mL of water according to randomized dosing schedule. Water intake was restricted from 1.0 hour prior to and 1.0 hour after drug administration. To facilitate urine flow and to compensate for water loss due to the diuretic effect of the drug, subjects were encouraged to consume 240 mL of fluid each hour while awake until 48 hours after dose administration. Standard meals were provided at appropriate times thereafter.

F. **SUBJECT MONITORING**:

Vital signs (blood pressure and heart rates) were monitored predose (-1 hr) and at 1, 6, 12, 24 and 48 hours post-dose (the values were reported in vol. #A1.4, section "Attachment").

G. **Sample Collection**:

1. Blood Samples:
Blood samples were collected at 0 (pre-dose), 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24, 36 and 48 hours. Plasma was separated and promptly frozen for analysis of hydroxytriamterene and triamterene sulfate.

2. Urine samples:
Urine samples were collected over the period of 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-24, 24-36, and 36-48 hours for hydrochlorothiazide analysis.

H. **ASSAY METHODOLOGY**:

I. **IN VIVO RESULTS**:

Thirty two (32) healthy male subjects were enrolled in the study and all subjects successfully completed the study. The data set used for statistical analyses contained data from 32 subjects (#1-32).

J. **Adverse Reactions**:

The adverse reactions have been reported (ANDA #74821, vol. A1.4, Section "Final Report", pages #25-27) by the subjects. Non of the adverse reactions were considered serious or resulted in dropping any subject from study participation. The adverse reactions are summarized as follows:

Type of Adverse Reactions	Test Prod.	Reference Prod.
Headache	8 subjects	6 subjects
Fever	--	2
Hot Flushes	--	1
Dry Mouth	1	--
Pharyngitis (sore throat)	5	4
Purpura (hematoma)	1	1
Respiratory Disorder (head congestion)	--	2
Rhinitis (Stuffy Nose)	1	1
Increased Sweating	--	2
Syncope (Fainting)	1	--

K. **DATA ANALYSIS**:

The pharmacokinetic parameters hydroxytriamterene, triamterene and hydrochlorothiazide were analyzed using ANOVA. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects. The 90% confidence intervals and the ratios of the test/reference means were also determined. The pharmacokinetics parameters for hydroxytriamterene,

triamterene and hydrochlorothiazide under fasting conditions are summarized in the tables below:

Table 1
Mean Plasma Concentrations (ng/mL) of Hydroxytriamterene in 32 Subjects Following 1X37.5 mg/25 mg Oral Dose of Triamterene/ Hydrochlorothiazide Under Fasting Conditions

Time HR	Test	SD1	Reference	SD2	Mean T/R
0	0.00	0.00	0.00	0.00	.
0.33	165.48	182.13	133.70	128.93	1.24
0.5	573.32	328.83	568.42	348.93	1.01
0.75	1005.10	409.16	1081.64	415.99	0.93
1	**1161.72**	477.32	**1214.09**	433.96	**0.96**
1.25	1059.31	424.32	1144.97	379.75	0.93
1.5	934.47	352.40	1021.94	305.65	0.91
2	690.72	240.16	765.41	225.98	0.90
3	395.13	129.62	430.91	125.33	0.92
4	242.83	83.77	256.00	62.96	0.95
6	134.50	47.82	134.43	35.34	1.00
8	64.48	22.27	65.30	20.21	0.99
10	37.03	13.62	37.29	13.21	0.99
12	24.33	9.33	23.27	8.11	1.05
14	16.43	8.70	15.42	6.72	1.07
24	7.10	11.11	4.33	9.01	1.64
36	1.85	5.10	1.81	5.04	1.02
48	0.86	3.40	0.00	0.00	.

Table 2
Summary of Pharmacokinetics Parameters (Hydroxytriamterene) in 32 Subjects Following 1X37.5 mg/25 mg Oral Dose of Triamterene/Hydrochlorothiazide Under Fasting Conditions

	Test	SD1	Reference	SD2	Mean T/R
AUCT	3255.34	680.66	3397.97	625.88	**0.96**
AUCI	3363.09	617.15	3494.09	601.41	**0.96**
CMAX	1212.47	446.75	1280.16	417.22	**0.95**
KE	0.22	0.10	0.25	0.10	0.90
THALF	5.48	6.59	4.67	5.17	1.17
TMAX	1.06	0.44	1.10	0.36	0.96
***LAUCT**	**3180.65**	0.22	**3340.01**	0.19	**0.95**
***LAUCI**	**3305.79**	0.19	**3441.85**	0.18	**0.96**
***LCMAX**	**1102.99**	0.49	**1194.71**	0.42	**0.92**

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the

logs).

Table 3
LSMeans and 90% Confidence Intervals
(Hydroxytriamterene)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCT	3255.34	3397.97	90.59	101.01
AUCI	3363.09	3494.09	92.06	100.44
CMAX	1212.47	1280.16	85.27	104.15
***LAUCT**	3180.65	3340.01	**89.89**	**100.88**
***LAUCI**	3305.79	3441.85	**91.89**	**100.40**
***LCMAX**	1102.99	1194.71	**80.94**	**105.31**

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML
* The values represent the geometric means (antilog of the means of the logs).

1. The mean plasma hydroxtriamterene levels reached a maximum level of concentration around 1.0 hour (Table #1 and the attached Figures #1&2).

2. The arithmetic test/reference mean ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were 0.96, 0.96 and 0.95, respectively. The geometric test/reference mean ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were 0.95, 0.96 and 0.92, respectively (Table #2). The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within the acceptable range of 80-125% (Table #3).

   There were no significant sequence, period or treatment effects for the log-transformed of the test and reference drug treatments for hydroxytriamterene pharmacokinetic parameters AUC_{0-t}, AUC_{0-} and C_{max}.

3. Hydroxytriamterene average values of $T_{1/2}$, T_{max} and K_{el} for the test product were comparable to the corresponding reference values (Table #2).

Table 4
Mean Plasma Concentrations (ng/mL)
of Triamterene in 32 Subjects Following 1X37.5 mg/25 mg
Oral Dose of Triamterene/Hydrochlorothiazide
Under Fasting Conditions

TIME HR	Test	SD1	Reference	SD2	Mean T/R
0	0.00	0.00	0.00	0.00	.
0.33	36.31	35.77	33.99	26.31	1.07
0.5	69.41	34.86	70.67	39.67	0.98
0.75	**84.99**	37.46	**83.33**	30.33	**1.02**
1	81.64	32.70	79.61	23.80	1.03
1.25	71.66	25.57	75.45	21.45	0.95
1.5	65.27	22.41	70.72	19.84	0.92
2	52.69	18.46	57.53	18.00	0.92
3	36.29	15.14	39.11	13.09	0.93
4	24.64	11.29	25.61	8.94	0.96
6	11.43	8.40	11.46	5.80	1.00
8	5.50	4.24	5.75	3.79	0.96
10	2.83	2.87	2.80	3.02	1.01
12	0.81	2.04	0.75	2.20	1.09
14	0.47	1.41	0.28	1.59	1.66
24	0.37	1.01	0.38	1.65	0.97
36	0.00	0.00	0.14	0.77	0.00
48	0.00	0.00	0.06	0.36	0.00

Table 5
Summary of Pharmacokinetics Parameters (Triamterene)
in 32 Subjects Following 1X37.5 mg/25 mg
Oral Dose of Triamterene/Hydrochlorothiazide
Under Fasting Conditions

	Test	SD1	Reference	SD2	Mean T/R
AUCI	272.44	88.15	284.78	91.43	**0.96**
AUCT	263.47	88.73	276.15	88.07	**0.95**
CMAX	96.65	34.59	95.30	30.84	**1.01**
KE	0.37	0.10	0.38	0.08	0.96
THALF	2.19	1.33	2.15	2.06	1.02
TMAX	0.86	0.53	0.99	0.39	0.87
***LAUCI**	**257.99**	0.35	**271.32**	0.32	**0.95**
***LAUCT**	**247.83**	0.37	**262.83**	0.32	**0.94**
***LCMAX**	**89.38**	0.43	**90.19**	0.35	**0.99**

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

Table 6
LSMeans and 90% Confidence Intervals
(Triamterene-Under Fasting Conditions)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCI	272.44	284.78	89.11	102.22
AUCT	263.47	276.15	88.48	102.34
CMAX	96.65	95.30	90.79	112.05
***LAUCI**	257.99	271.32	**87.91**	**102.85**
***LAUCT**	247.83	262.83	**86.49**	**102.80**
***LCMAX**	89.38	90.19	**86.37**	**113.71**

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML
* The values represent the geometric means (antilog of the means of the logs).

1. The mean plasma triamterene levels reached a maximum level of concentration around 0.75 hour (Table #4 and the attached Figures #3&4).

2. The arithmetic test/reference mean ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were 0.95, 0.96 and 1.01, respectively. The geometric test/reference mean ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were 0.94, 0.95 and 0.99, respectively (Table #5). The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within the acceptable range of 80-125% (Table #6).

   There were no significant sequence, period or treatment effects for the log-transformed of the test and reference drug treatments for triamterene pharmacokinetic parameters AUC_{0-t}, AUC_{0-} and C_{max}.

3. Triamterene average values of $T_{1/2}$, T_{max} and K_{el} for the test product were comparable to the corresponding reference values (Table #5).

Table 7
MEAN URINARY EXCRETION FOR TEST AND REFERENCE PRODUCTS FOR HYDROCHLOROTHIAZIDE Under Fasting Conditions

TIME HR	Test	SD1	Reference	SD2	Mean T/R
0	0.00	0.00	0.00	0.00	.
1	2.56	1.42	2.63	1.31	0.97
3	5.46	1.28	5.56	1.41	0.98
5	2.85	1.08	3.10	1.04	0.92
7	1.50	0.41	1.61	0.46	0.93
9	1.14	0.56	1.22	0.39	0.94
11	0.64	0.31	0.65	0.28	0.98
13	0.36	0.27	0.50	0.29	0.72
18	1.56	0.78	1.70	0.53	0.92
30	0.11	0.64	0.00	0.00	.
42	0.00	0.00	0.00	0.00	.

UNIT: URINARY EXCRETION=MCG TIME=HRS
Note: The time shown in the tables is represented by a mid-point of each urine collection interval.

Table 8
CUMULATIVE URINARY EXCRETION FOR HYDROCHLOROTHIAZIDE Under Fasting Conditions

TIME HR	Test	SD1	Reference	SD2	Mean T/R
0	0.00	0.00	0.00	0.00	.
1	2.56	1.42	2.63	1.31	0.97
3	8.02	2.29	8.19	2.03	0.98
5	10.87	2.65	11.30	2.51	0.96
7	12.38	2.79	12.91	2.60	0.96
9	13.52	3.02	14.13	2.76	0.96
11	14.16	3.15	14.78	2.77	0.96
13	14.52	3.18	15.28	2.87	0.95
18	16.08	3.55	16.98	3.03	0.95
30	16.19	3.66	16.98	3.03	0.95
42	16.19	3.66	16.98	3.03	0.95

UNIT: URINARY EXCRETION=MCG TIME=HRS

Table 9
TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION) FOR HYDROCHLOROTHIAZIDE UNDER FASTING CONDITIONS

PARAMETER	Test	SD1	Reference	SD2	Mean T/R
CUM	16.19	3.66	16.98	3.03	0.95
***LCUM**	**15.73**	0.26	**16.69**	0.19	**0.94**
RMAX	2.77	0.64	2.86	0.67	0.97
***LRMAX**	**2.69**	0.27	**2.77**	0.25	**0.97**
RTMAX	3.00	0.51	2.94	0.62	1.02
*LRTMAX	2.95	0.22	2.85	0.29	1.03

* The values represent the geometric means (antilog of the means of the logs).
UNIT: CUM=MCG RMAX=MG/HR RTMAX=HR

Table 10
LSMEANS AND 90% CONFIDENCE INTERVALS FOR HYDROCHLOROTHIAZIDE UNDER FASTING CONDITIONS

PARAMETER	LSMEAN1	LSMEAN2	LOW CI12	UPP CI12
CUM	16.19	16.98	90.40	100.40
***LCUM**	15.73	16.69	**88.77**	**100.05**
RMAX	2.77	2.86	89.63	104.53
***LRMAX**	2.69	2.77	**88.74**	**105.81**
RTMAX	3.00	2.94	94.05	110.20
*LRTMAX	2.95	2.85	92.80	115.42

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
* The values represent the geometric means (antilog of the means of the logs).
UNIT: CUM=MCG RMAX=MCG/HR RTMAX=HR

Hydrochlorothiazide Urine Data Analysis (under fasting conditions):

1. The mean urinary excretion and cumulative excretion, respectively, are presented in Tables 7&8 and Figures 5&6. The urinary excretion data for the test and reference products are comparable as shown by T/R ratios (Table #7).

2. The average means of the log-transformed cumulative urinary excretion (LCUM) and log-transformed maximum urinary excretion rate (LRMAX) of the test and reference drug products are comparable (Table 9). The 90% confidence intervals for the log-transformed LCUM and LRMAX were within acceptable range of 80-125% (Table 10).

V. SINGLE DOSE BIOEQUIVALENCE STUDY, UNDER NON-FASTING CONDITIONS

A. **Sponsor:**
Geneva Pharmaceuticals, Inc.
2555 West Midway Blvd.
Broomfield, CO 80038-0469

Study site
Clinical and Analytical Facilities
The same as the protocol under fasting conditions

Study Dates:
Phase I: August 16, 1995 to August 18, 1995
Phase II: August 23, 1995 to August 25, 1995
Phase III: August 30, 1995 to September 01, 1995

B. **Study design:**
Randomized, three-way single dose crossover study, under non-fasting conditions.

C. Subjects:
Eighteen (18) healthy male subjects were enrolled in the study and all subjects (#1-18) completed the clinical study. There were no dropouts over the course of the study.

Subject Exclusion and Restriction Criteria:
Same as under fasting conditions.

D. **Treatment:**

Test Product:
Treatment 1: 1 x 37.5 mg/25 mg Geneva's Triamterene/Hydrochlorothiazide capsules, lot # 6495058, lot size capsules, potency 94.9% and 96.4%, content uniformity 95.8% (CV=3.3%) and 95.3% (CV=3.0%), for triamterene and hydrochlorothiazide, respectively. Treatment #1 was administered under fasting conditions.

Treatment 2: 1 x 37.5 mg/25 mg Geneva's Triamterene/Hydrochlorothiazide capsules, lot # 6495058, lot size capsules, potency 94.9% and 96.4%, content uniformity 95.8% (CV=3.3%) and 95.3% (CV=3.0%), for triamterene and hydrochlorothiazide, respectively. Treatment #2 was administered under non-fasting conditions.

Reference Product:
Treatment 3: 1 x 37.5 mg/25 mg SmithKline Beecham's Dyazide^{R} capsules 37.5 mg/25 mg, lot #224E50, potency 96.4% and 100%, content uniformity 99.8% (CV=1.8%) and 95.2% (CV=3.5%), for triamterene and hydrochlorothiazide, respectively. The expiration date: 6/96. Treatment #3 was administered under non-fasting conditions.

Washout period: 7 days

E. **Drug, Food and Fluid Intake**:

Subjects who received treatment 1, fasted overnight for 9.5 hours before dosing and for 4 hours after drug administration. Subjects who were fed standard recommended breakfast prior to dosing (treatments 2 and 3) only fasted for 9.5 hours. Treatments 2 and 3 differed from treatment 1 in that the subjects were fed a standard high fat breakfast, which was consumed in its entirety 30 minutes before drug administration. The standard breakfast meal contained the following: one buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, one serving of hashed brown potatoes, eight fluid ounces (240 ml) of whole milk and six fluid ounces (180 ml) of orange juice. Each dose was followed by 8 fluid ounces (240 mL) of room temperature tap water according to randomized dosing schedule. To facilitate urine flow and to compensate for water loss due to the diuretic effect of the drug, subjects were encouraged to consume 240 mL of fluid each hour while awake until 48 hours after dose administration. Standard meals were provided at appropriate times thereafter.

F. **Assay Methodology**:

Methods and Validation:

Same as under fasting conditions.

G. **Sample Collection**:

1. Blood Samples:

Blood samples were collected at 0 (pre-dose), 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24, 36 and 48 hours. Plasma was separated and promptly frozen for analysis of hydroxytriamterene and triamterene.

2. Urine samples:

Urine samples were collected over the period of 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-24, 24-36, and 36-48 hours for hydrochlorothiazide analysis.

H. **Adverse Reactions**:

The adverse reactions have been reported (ANDA #74821, vol. C1.10, Section "Final Report", page #26) by the subjects. None of the adverse reactions was considered serious or resulted in dropping any subject from study participation. The adverse reactions are summarized as follows:

Type of Adverse Reactions	Test Prod.	Reference Prod.
Abdominal Pain	1	--
Asthenia (heat exhaustion)	1	--
Earache	1	--
Headache	6	3
Myalgia (sore beck)	1	--
Nausea	--	1
Pressure behind both eyes	2	--
Rhinitis (stuffy nose)	1	--

I. **In Vivo Results**:

Eighteen (18) healthy male subjects who enrolled in the study completed the clinical study. There were no dropouts over the course of the study. The pharmacokinetics parameters for hydroxytriamterene, triamterene and hydrochlorothiazide under non-fasting conditions are summarized in the tables below:

Table 11
Mean Plasma Concentrations (ng/mL)
of Hydroxytriamterene in 18 Subjects Following
1X37.5 mg/25 mg Oral Dose of Triamterene/
Hydrochlorothiazide Under Non-Fasting Conditions

TIME HR	**MEAN1**	SD1	**MEAN2**	SD2	**MEAN3**	SD3
0	0.00	0.00	0.00	0.00	0.00	0.00
0.33	149.11	124.20	2.47	10.49	1.98	6.12
0.5	580.35	322.69	14.37	40.43	12.50	28.05
0.75	1081.24	349.94	58.99	129.31	63.36	110.36
1	**1216.29**	275.06	114.69	181.99	162.58	222.98
1.25	1134.06	234.47	209.62	233.41	267.18	261.13
1.5	984.12	203.36	363.38	282.81	416.97	286.55
2	761.18	181.16	586.72	282.35	628.03	264.25
3	428.82	94.33	**718.06**	177.56	**773.94**	206.59
4	274.53	65.29	609.67	118.53	634.33	191.61
6	150.27	35.66	332.56	145.68	307.39	113.59
8	93.13	67.19	146.72	56.83	142.13	59.97
10	44.82	12.46	74.78	27.75	75.63	33.38
12	27.46	8.54	40.86	14.13	41.50	16.19
14	18.97	8.28	23.91	7.67	25.14	9.95
24	3.86	8.06	1.17	4.95	2.89	5.72
36	0.61	2.52	0.00	0.00	0.00	0.00
48	0.00	0.00	0.00	0.00	0.00	0.00

(CONTINUED)

TIME HR	RMEAN1/2	RMEAN1/3	**RMEAN2/3**
0	.	.	.
0.33	60.31	75.18	1.25
0.5	40.38	46.43	1.15
0.75	18.33	17.06	0.93
1	10.60	7.48	0.71
1.25	5.41	4.24	0.78
1.5	2.71	2.36	0.87
2	1.30	1.21	0.93
3	0.60	0.55	**0.93**
4	0.45	0.43	0.96
6	0.45	0.49	1.08
8	0.63	0.66	1.03
10	0.60	0.59	0.99
12	0.67	0.66	0.98

14	0.79	0.75	0.95
24	3.31	1.34	0.40
36	.	.	.
48	.	.	.

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Reference-Fed
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 12
Summary of Pharmacokinetics Parameters (Hydroxytriamterene) in 18 Subjects Following 1X37.5 mg/25 mg Oral Dose of Triamterene/Hydrochlorothiazide Under Non-Fasting Conditions

PARAMETER	MEAN1	SD1	**MEAN2**	SD2	**MEAN3**	SD3
AUCI	3583.88	743.04	3622.72	500.15	3767.61	557.65
AUCT	3508.76	718.87	3536.61	464.27	3693.61	536.88
CMAX	1266.82	294.94	807.44	178.04	859.06	146.88
KE	0.27	0.06	0.30	0.06	0.28	0.07
THALF	3.09	1.51	2.58	1.55	2.73	1.19
TMAX	1.00	0.25	3.28	1.18	3.01	1.06
***LAUCI**	3517.90	0.19	**3590.31**	0.14	**3730.01**	0.14
***LAUCT**	3445.69	0.19	**3507.62**	0.13	**3657.97**	0.14
***LCMAX**	1234.15	0.24	**789.72**	0.22	**846.36**	0.18

(CONTINUED)

PARAMETER	RMEAN1/2	RMEAN1/3	**RMEAN2/3**
AUCI	0.99	0.95	0.96
AUCT	0.99	0.95	0.96
CMAX	1.57	1.47	0.94
KE	0.88	0.94	1.07
THALF	1.19	1.13	0.95
TMAX	0.31	0.33	1.09
***LAUCI**	0.98	0.94	**0.96**
***LAUCT**	0.98	0.94	**0.96**
***LCMAX**	1.56	1.46	**0.93**

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Reference-Fed
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR

1. Under non-fasting conditions, the mean plasma levels for hydroxytriamterene reached the maximum around 3.0 hours (Table 11 and Figures 7&8).

2. The test/reference mean ratios under non-fasting conditions for the AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} (Table 12) were within the acceptable range of 0.8 to 1.2 that has been set by the Division of Bioequivalence.

3. Under non-fasting conditions the hydroxytriamterene average values of $T_{1/2}$, T_{max} and K_{el} for the test product were comparable to the reference product values (Table 12).

Table 13
Mean Plasma Concentrations (ng/mL)
of Triamterene in 18 Subjects Following 1X37.5 mg/25 mg
Oral Dose of Triamterene/Hydrochlorothiazide
Under Non-Fasting Conditions

TIME HR	MEAN1	SD1	**MEAN2**	SD2	**MEAN3**	SD3
0	0.00	0.00	0.00	0.00	0.00	0.00
0.33	47.45	34.89	0.42	1.77	0.64	2.25
0.5	85.72	43.80	2.01	4.15	2.25	4.77
0.75	**115.60**	39.67	7.01	9.91	9.96	14.90
1	106.32	38.21	12.97	14.66	17.37	20.06
1.25	97.67	31.16	25.28	20.93	28.91	22.61
1.5	86.97	25.20	39.63	25.22	42.10	25.04
2	72.37	22.12	56.15	25.42	57.41	24.01
3	47.63	14.72	**64.54**	25.64	**69.02**	25.24
4	33.90	10.51	57.31	19.06	61.26	24.87
6	14.28	4.62	30.28	14.62	29.57	13.98
8	7.60	2.66	14.34	7.10	13.91	7.09
10	4.15	1.47	7.17	3.22	7.29	3.66
12	1.89	1.47	3.48	2.20	3.47	2.20
14	0.83	1.23	1.49	1.45	1.74	1.51
24	0.00	0.00	0.00	0.00	0.00	0.00
36	0.00	0.00	0.00	0.00	0.00	0.00
48	0.00	0.00	0.00	0.00	0.00	0.00

(CONTINUED)

TIME HR	RMEAN1/2	RMEAN1/3	**RMEAN2/3**
0	.	.	.
0.33	113.73	74.33	0.65
0.5	42.69	38.16	0.89
0.75	16.49	11.61	0.70
1	8.20	6.12	0.75
1.25	3.86	3.38	0.87
1.5	2.19	2.07	0.94
2	1.29	1.26	0.98
3	0.74	0.69	**0.94**
4	0.59	0.55	0.94
6	0.47	0.48	1.02
8	0.53	0.55	1.03
10	0.58	0.57	0.98
12	0.54	0.54	1.00
14	0.56	0.48	0.86
24	.	.	.

36	.	.	.
48	.	.	.

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Reference-Fed
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 14
Summary of Pharmacokinetics Parameters (Triamterene) in 18 Subjects Following 1X37.5 mg/25 mg Oral Dose of Triamterene/Hydrochlorothiazide Under Non-Fasting Conditions

PARAMETER	MEAN1	SD1	**MEAN2**	SD2	**MEAN3**	SD3
AUCI	359.06	105.90	338.00	102.82	352.00	**98.24**
AUCT	350.00	105.89	330.11	102.78	343.61	**97.89**
CMAX	121.87	41.43	71.71	21.98	77.12	**20.19**
KE	0.31	0.07	0.35	0.03	0.34	**0.05**
THALF	2.44	0.79	1.99	0.17	2.11	**0.35**
TMAX	0.86	0.27	3.19	1.25	2.92	1.24
***LAUCI**	342.77	0.33	**321.19**	0.34	**338.17**	0.30
***LAUCT**	333.22	0.34	**312.81**	0.35	**329.49**	0.31
***LCMAX**	113.94	0.41	**67.99**	0.36	**74.34**	0.29

(CONTINUED)

PARAMETER	RMEAN1/2	RMEAN1/3	**RMEAN2/3**
AUCI	1.06	1.02	0.96
AUCT	1.06	1.02	0.96
CMAX	1.70	1.58	0.93
KE	0.87	0.91	1.04
THALF	1.23	1.16	0.95
TMAX	0.27	0.30	1.10
***LAUCI**	1.07	1.01	**0.95**
***LAUCT**	1.07	1.01	**0.95**
***LCMAX**	1.68	1.53	**0.91**

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Reference-Fed
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR

1. Under non-fasting conditions, the mean plasma levels for triamterene reached the maximum around 3.0 hours (Table #13 and Figures # 9&10).

2. The test/reference mean ratios under non-fasting conditions for the AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} (Table 14) were within the acceptable range of 0.8 to 1.2 that has been set by the Division of Bioequivalence.

3. Under non-fasting conditions the triamterene average values of $T_{1/2}$, T_{max} and K_{el} for the test product were comparable to the reference product values (Table 14).

Table #15
MEAN URINARY EXCRETION FOR TEST AND REFERENCE PRODUCTS for HYDROCHLOROTHIAZIDE UNDER Non-Fasting Conditions

TIME HR	MEAN1	SD1	**MEAN2**	SD2	**MEAN3**	SD3
0	0.00	0.00	0.00	0.00	0.00	0.00
1	2.88	1.00	0.34	0.48	0.49	0.55
3	5.20	1.02	4.21	1.32	4.67	1.39
5	2.82	0.60	4.25	1.16	4.50	1.11
7	1.68	0.29	2.55	0.46	2.53	0.52
9	1.14	0.18	1.42	0.23	1.48	0.32
11	0.85	0.24	0.99	0.20	1.09	0.26
13	0.29	0.33	0.45	0.38	0.60	0.34
18	1.78	0.21	1.91	0.31	1.85	0.53
30	0.00	0.00	0.00	0.00	0.00	0.00
42	0.00	0.00	0.00	0.00	0.00	0.00

(CONTINUED)

TIME HR	RMEAN1/2	RMEAN1/3	**RMEAN2/3**
0	.	.	.
1	8.47	5.88	0.69
3	1.23	1.11	0.90
5	0.66	0.63	0.94
7	0.66	0.67	1.01
9	0.81	0.77	0.95
11	0.86	0.78	0.91
13	0.63	0.48	0.76
18	0.93	0.96	1.03
30	.	.	.
42	.	.	.

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Reference-Fed
UNIT: URINARY EXCRETION=MCG TIME=HRS
Note: The time shown in the tables is represented by a mid-point of each urine collection interval.

Table #16
CUMULATIVE URINARY EXCRETION FOR HYDROCHLOROTHIAZIDE UNDER NON-Fasting CONDITIONS

TIME HR	MEAN1	SD1	**MEAN2**	SD2	**MEAN3**	SD3
0	0.00	0.00	0.00	0.00	0.00	0.00
1	2.88	1.00	0.34	0.48	0.49	0.55
3	8.08	1.49	4.55	1.59	5.16	1.75
5	10.90	1.61	8.80	1.71	9.66	2.05
7	12.58	1.59	11.35	1.74	12.19	1.95
9	13.72	1.59	12.77	1.76	13.67	1.91
11	14.57	1.50	13.75	1.81	14.76	1.87
13	14.86	1.51	14.21	1.99	15.36	1.94
18	16.64	1.55	16.12	1.99	17.21	2.04
30	16.64	1.55	16.12	1.99	17.21	2.04
42	16.64	1.55	16.12	1.99	17.21	2.04

(CONTINUED)

TIME HR	RMEAN1/2	RMEAN1/3	**RMEAN2/3**
0	.	.	.
1	8.47	5.88	0.69
3	1.78	1.57	0.88
5	1.24	1.13	0.91
7	1.11	1.03	0.93
9	1.07	1.00	0.93
11	1.06	0.99	0.93
13	1.05	0.97	0.93
18	1.03	0.97	0.94
30	1.03	0.97	0.94
42	1.03	0.97	0.94

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Reference-Fed
UNIT: URINARY EXCRETION=MCG TIME=HRS

Table 17
TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION) FOR HYDROCHLOROTHIAZIDE UNDER NON-Fasting CONDITIONS

PARAMETER	MEAN1	SD1	**MEAN2**	SD2	**MEAN3**	SD3
CUM	16.64	1.55	16.12	1.99	17.21	2.04
***LCUM**	16.57	0.09	**16.00**	0.12	**17.09**	0.12
***LRMAX**	2.57	0.20	**2.45**	0.17	**2.60**	0.20
*LTMAX	2.66	0.36	4.22	0.25	3.95	0.29
RMAX	2.61	0.49	2.48	0.43	2.65	0.51
TMAX	2.78	0.65	4.33	0.97	4.11	1.23

(CONTINUED)

PARAMETER	RMEAN1/2	RMEAN1/3	**RMEAN2/3**
CUM	1.03	0.97	0.94
***LCUM**	1.04	0.97	**0.94**
***LRMAX**	1.05	0.99	**0.94**
*LTMAX	0.63	0.67	1.07
RMAX	1.05	0.99	0.94
TMAX	0.64	0.68	1.05

* The values represent the geometric means (antilog of the means of the logs).
UNIT: CUM=MCG RMAX=MG/HR RTMAX=HR

Hydrochlorothiazide Urine Data Analysis (under non-fasting conditions):

1. The mean urinary excretion and cumulative excretion, respectively, are presented in Tables 15&16 and Figures 11&12. The urinary excretion data for the test and reference products are comparable over the period of urine collection as shown by T/R ratios (Table #15).

2. The average means of the log-transformed cumulative urinary excretion (LCUM) and log-transformed maximum urinary excretion rate (LRMAX) of the test and reference drug products are comparable (Table #17). The test/reference mean ratios under non-fasting conditions for the LCUM and LRMAX (Table #17) were within the acceptable range of 0.8 to 1.2 that has been set by the Division of Bioequivalence.

V. **FORMULATION:**

Geneva's formulations for its Triamterene/Hydrochlorothiazide 37.5mg/25 mg capsules are shown below:

Table 18

Ingredients	Amount/Capsule
Triamterene USP	37.5
Hydrochlorothiazide USP	25
Lactose	
Povidone USP	
Sodium Starch Glycolate NF	
Glycine USP	
Citric Acid USP	
Polysorbate 80 NF	
Purified Water USP	
Magnesium Stearate NF	
#4 Opaque White Cap/Opaque White Body, Body and Cap	
Imprinted G 606 in Black Ink	
Total Capsule Weight	200.00 mg

VI. **In Vitro Dissolution Testing**

Method:	USP 23 apparatus 1 (basket) at 100 rpm
Medium:	900 mL of 0.1N HCL
Temperature:	37°C ± 0.5°C
No. Units Tested:	12
Sampling Time:	15, 30, 45 and 60 minutes
Methodology:	
Specification:	NLT (Q) is dissolved in 45 minutes
Test Product:	Geneva's triamterene/hydrochlorothiazide capsules 37.5mg/25 mg, lot # 6495058

Reference Product: SmithKline Beecham's Dyazide® capsules 37.5 mg/25 mg, lot #224E50

The dissolution testing results are presented in Table 20.

Table 19. In Vitro Dissolution Testing

Drug (Generic Name): Triamterene/Hydrochlorothiazide
Dose Strength: 37.5 mg/25 mg Capsules
ANDA No.:74-821
Firm: Geneva Pharmaceuticals Inc.
Submission Date: December 29, 1995
File Name: 74821SD.d95

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle:X RPM: 100
No. Units Tested: 12 Capsules
Medium:900 mL of 0.1N HCl
Specifications: NLT of the labeled amounts of triamterene and hydrochlorothiazide are dissolved in 45 minutes.
Reference Drug: SmithKline Beecham's Dyazide®
Assay Methodology:

II. Results of In Vitro Dissolution Testing: Triamterene

Sampling Times (min)	Test Product: Triamterene Lot # 6495058 Strength(mg) 37.5			Reference Product: Triamterene Lot # 224E50 Strength(mg) 37.5		
	Mean %	Range	%CV	Mean %	Range	%CV
15	85		4.0	80		6.9
30	95		2.8	93		3.2
45	97		3.0	97		2.5
60	98		2.9	99		1.8

Hydrochlorothiazide

Sampling Times (min)	Test Product: Hydrochlorothiazide Lot # 6495058 Strength(mg) 25			Reference Product: Hydrochlorothiazide Lot # 224E50 Strength(mg) 25		
	Mean %	Range	%CV	Mean %	Range	%CV
15	87		4.1	84		6.1
30	95		3.2	94		2.9
45	97		3.0	96		1.9
60	97		2.9	97		1.8

VII. COMMENTS:

1. Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, Triamterene/Hydrochlorothiazide Capsules, 37.5 mg/25 mg and the reference listed drug, SmithKline Beecham's Dyazide® capsules, 37.5 mg/25 mg are bioequivalent. The 90% confidence intervals for the log-transformed for the parameters AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, LCUM and LRMAX were all within the acceptable range of 80-125%.

2. Under non-fasting conditions: The in vivo bioequivalence study under non-fasting conditions demonstrated that the test product, the test product, Triamterene/Hydrochlorothiazide Capsules, 37.5 mg/25 mg and the reference listed drug, SmithKline Beecham's Dyazide® capsules, 37.5 mg/25 mg are bioequivalent. The ratios of the test mean to the reference mean for the AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, LCUM and LRMAX were within the acceptable range of 0.8 to 1.2.

VIII. DEFICIENCY:

1. The firm submitted dissolution data using the disolution medium 0.1N HCl, whereas the USP methodology specifies the medium should be 0.1 M acetic acid containing 1% of polysorbate 20. It should be noticed that the Division of Bioequivalence considers the current USP methodology to be the regulatory method which must be used for dissolution comparison. Therefore, the firm should resubmit the dissolution data for the test and reference drug products using the current USP methodology. The dissolution testing should be done on capsules from the same lot number that had been used in the in vivo bioequivalence study.

IX. RECOMMENDATIONS

1. The two in vivo bioequivalence studies conducted by Geneva Pharmaceuticals under fasting and non-fasting conditions on its drug product, Triamterene/Hydrochlorothiazide Capsules, 37.5 mg/25 mg (Lot #6495058), comparing it to the reference listed drug, SmithKline Beecham's Dyazide® capsules, 37.5 mg/25 mg (Lot #224E50) have been found acceptable by the Division of Bioequivalence. The two studies demonstrated that Geneva's Triamterene/Hydrochlorothiazide Capsules, 37.5 mg/25 mg are bioequivalent to the reference listed drug, SmithKline Beecham's Dyazide® capsules, 37.5 mg/25 mg. However, the application is incomplete for the reason given in the deficiency comment.

2. The dissolution testing data conducted by Geneva Pharmaceuticals on its drug product, Triamterene/Hydrochlorothiazide Capsules, 37.5 mg/25 mg (Lot #6495058) have been found incomplete. The firm is advised to resubmit the in vitro dissolution data in accordance with instruction indicated in the deficincy comment.

3. From the bioequivalence point of view, the firm has met the requirments

of the in vivo bioequivalence. However, the firm has not met the in vitro dissolution testing requirments for the reason given in the deficiency comment.

The firm should be informed of the deficiency comment and recommendations.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE 7/17/96

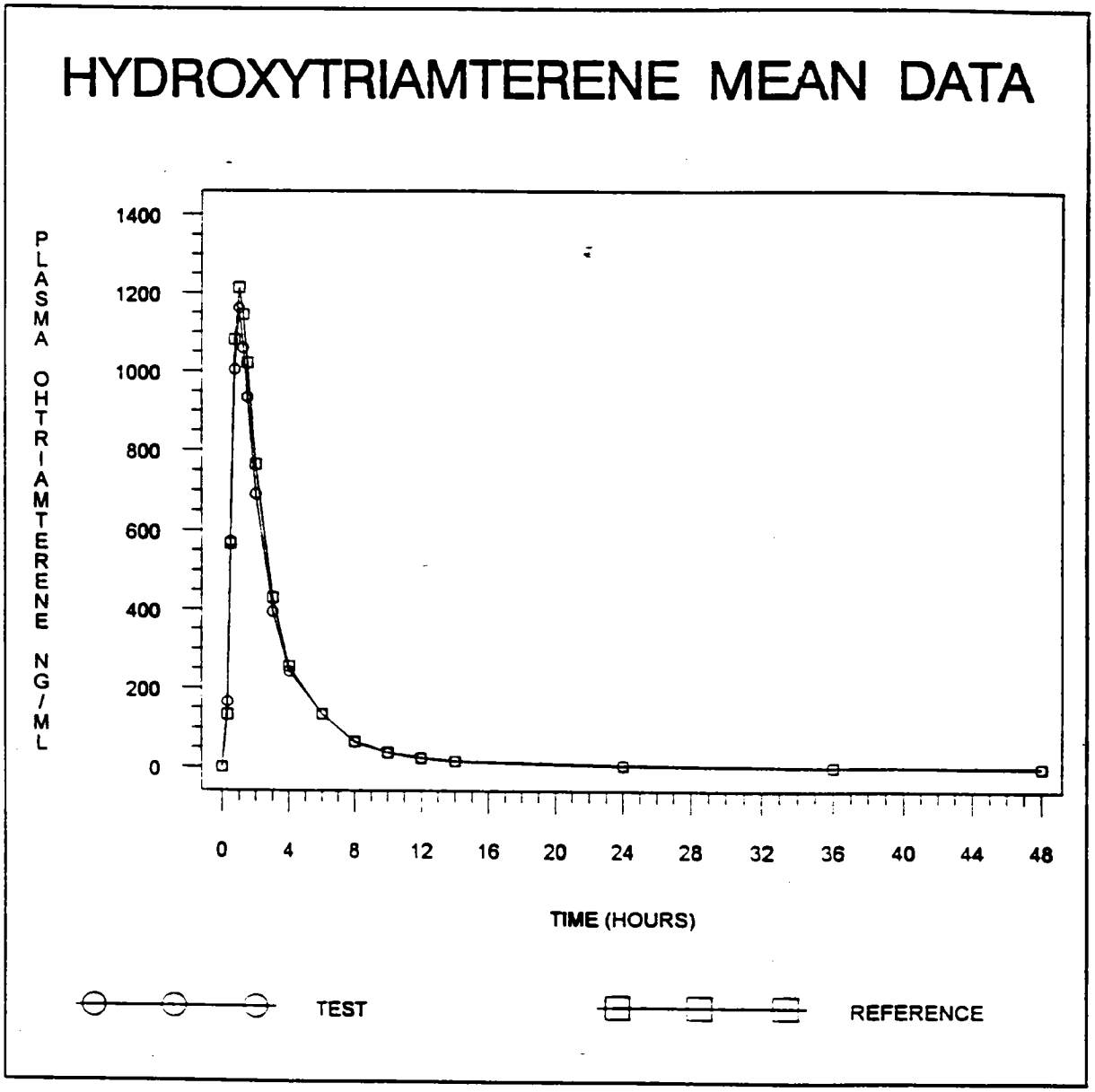
Concur: for Date: 7/18/96
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA 74-450 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Wahba), Drug File, Division File
ZZWahba/053196/062896/file #74450s.995

HCTZ/TRIAMTERENE FASTING STUDY
GENEVA B-07175

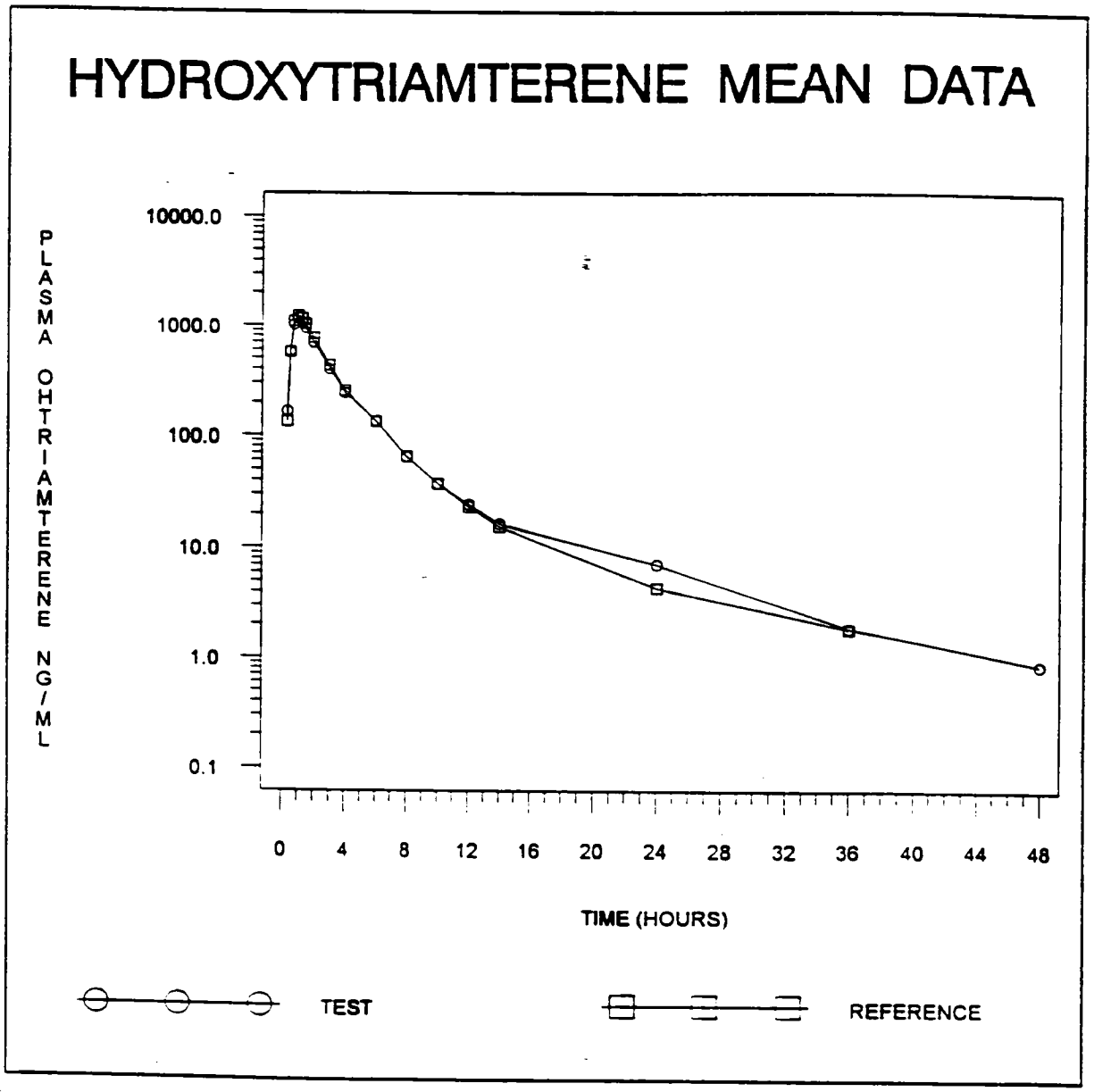
ANDA # 74-821

Figure #1 Linear Plot of Mean Plasma Hydroxytriamterene Concentrations *vs* Time



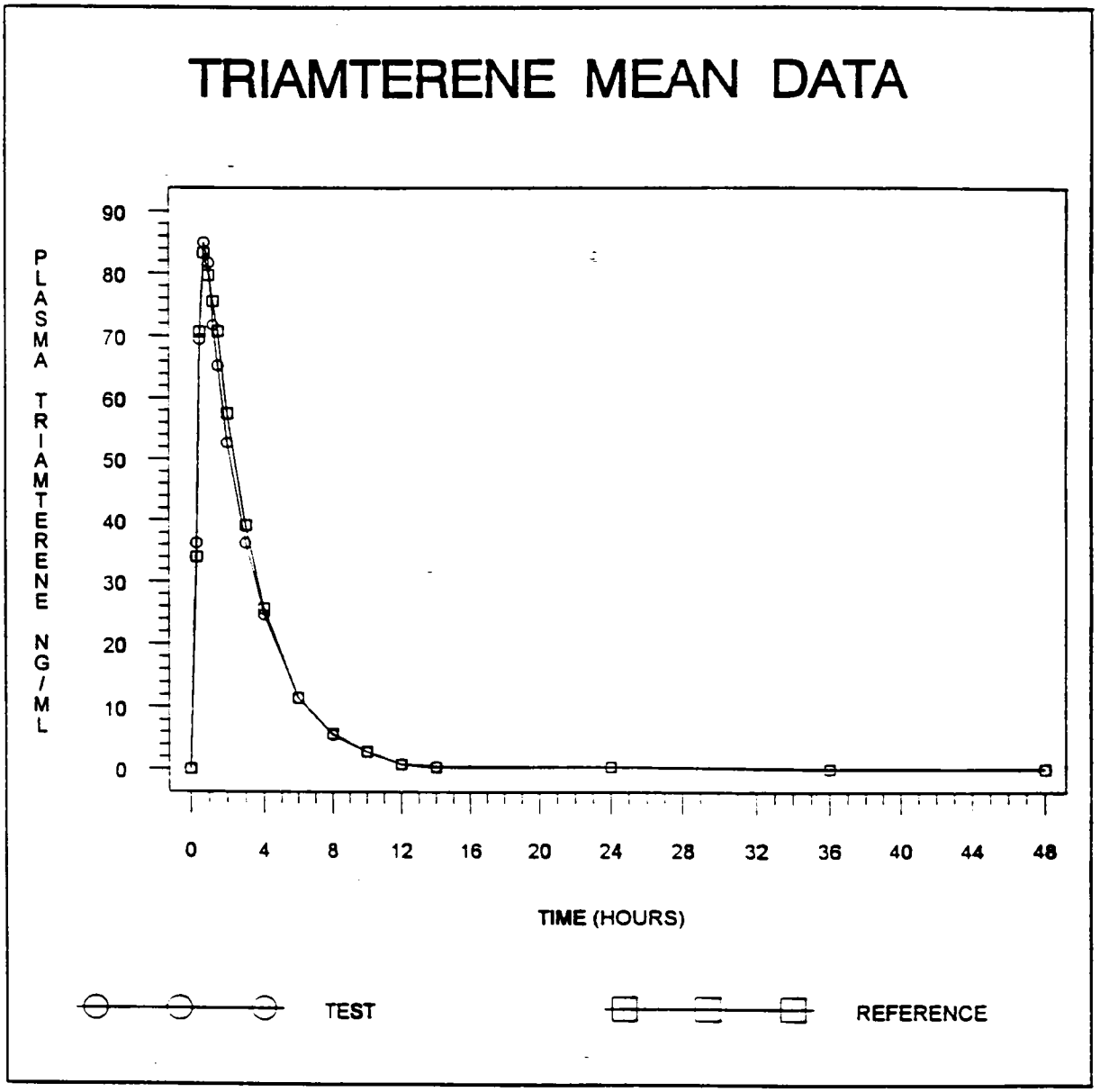
ANDA# 74-821

Figure #2 Semi-logarithmic Plot of Mean Plasma Hydroxytriamterene Concentrations *vs* Time



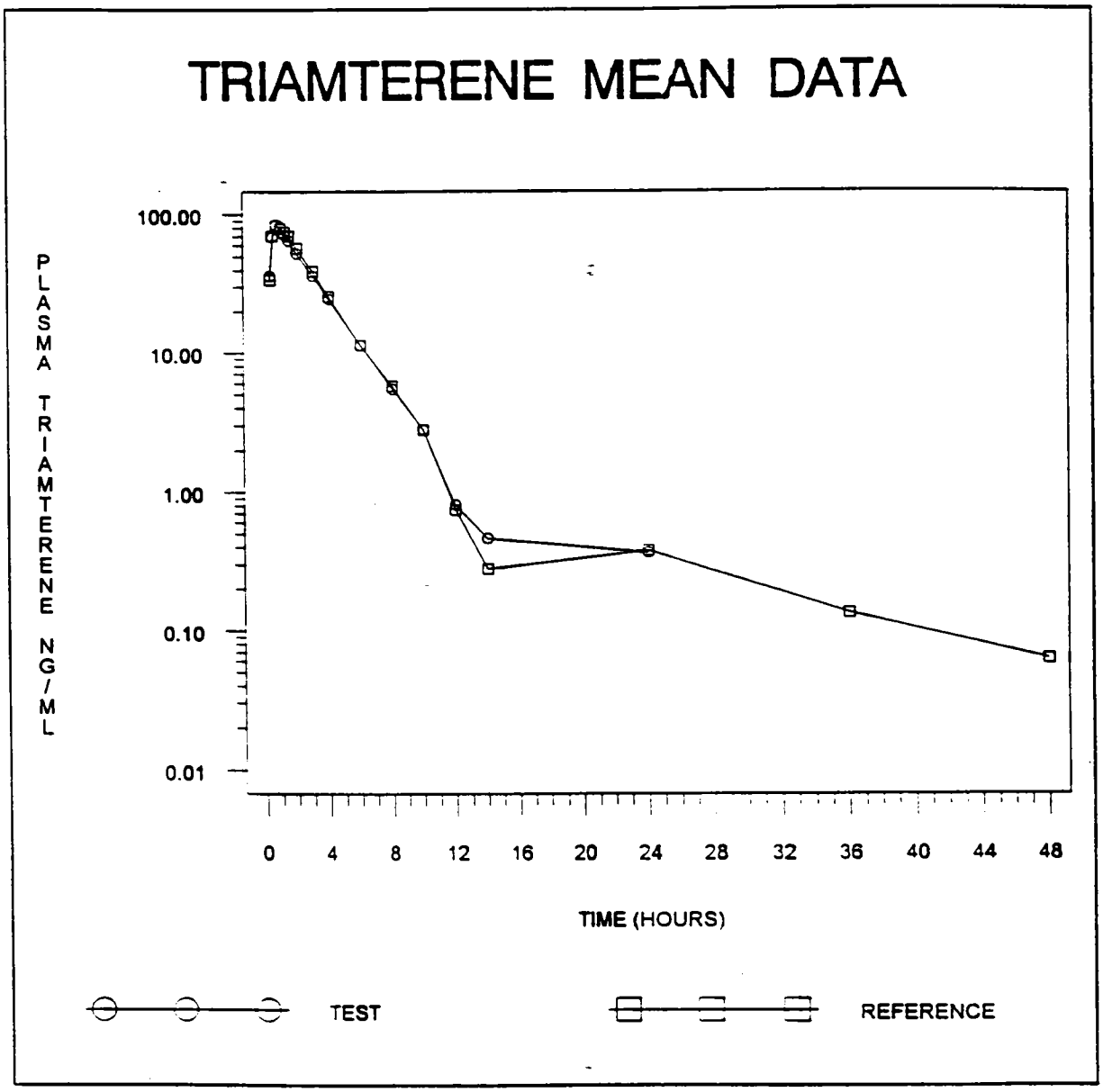
ANDA #74-821

Figure #3 Linear Plot of Mean Plasma Triamterene Concentrations *vs* Time



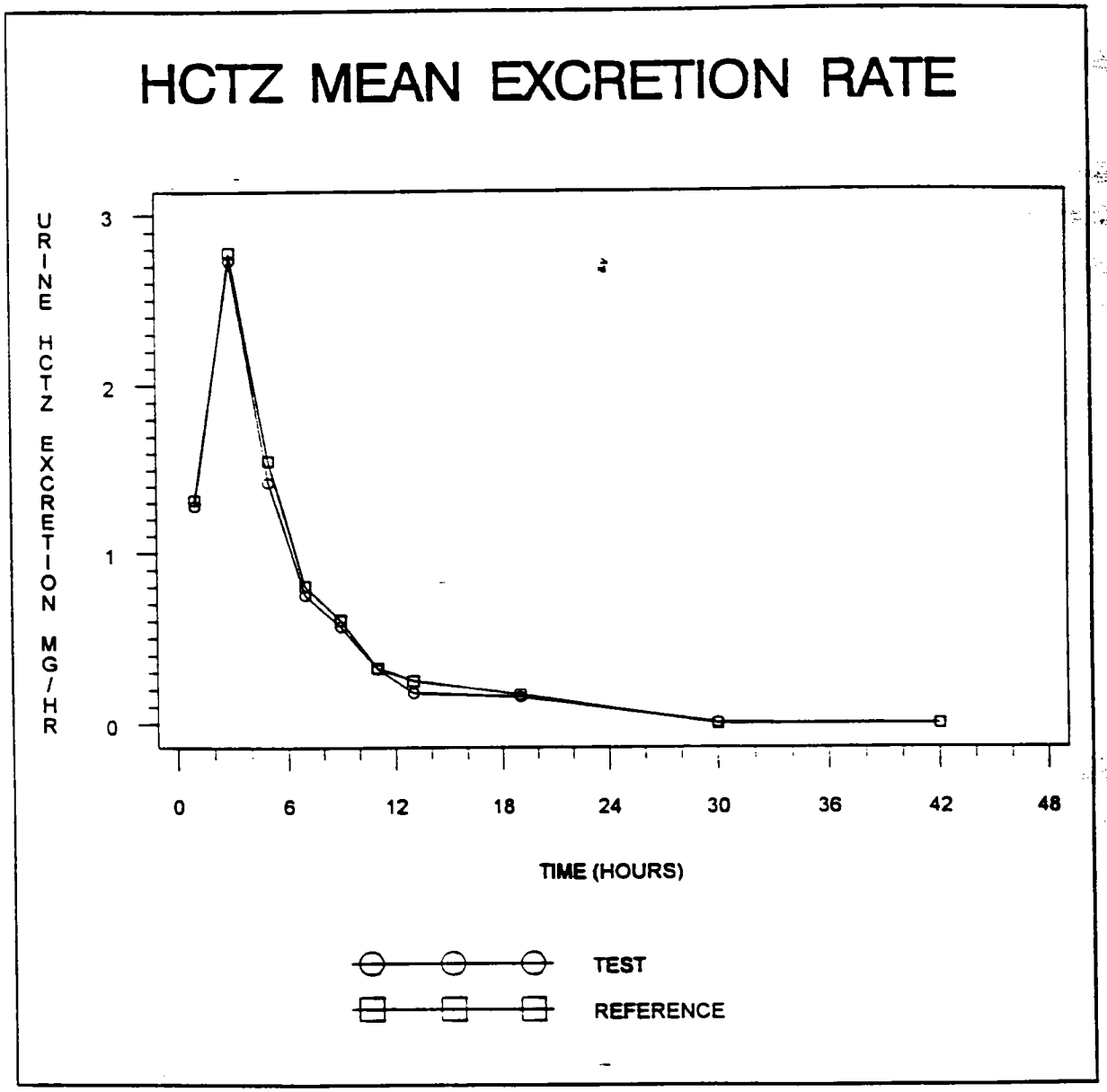
ANDA # 74-821

Figure # 4 Semi-logarithmic Plot of Mean Plasma Triamterene Concentrations *vs* Time



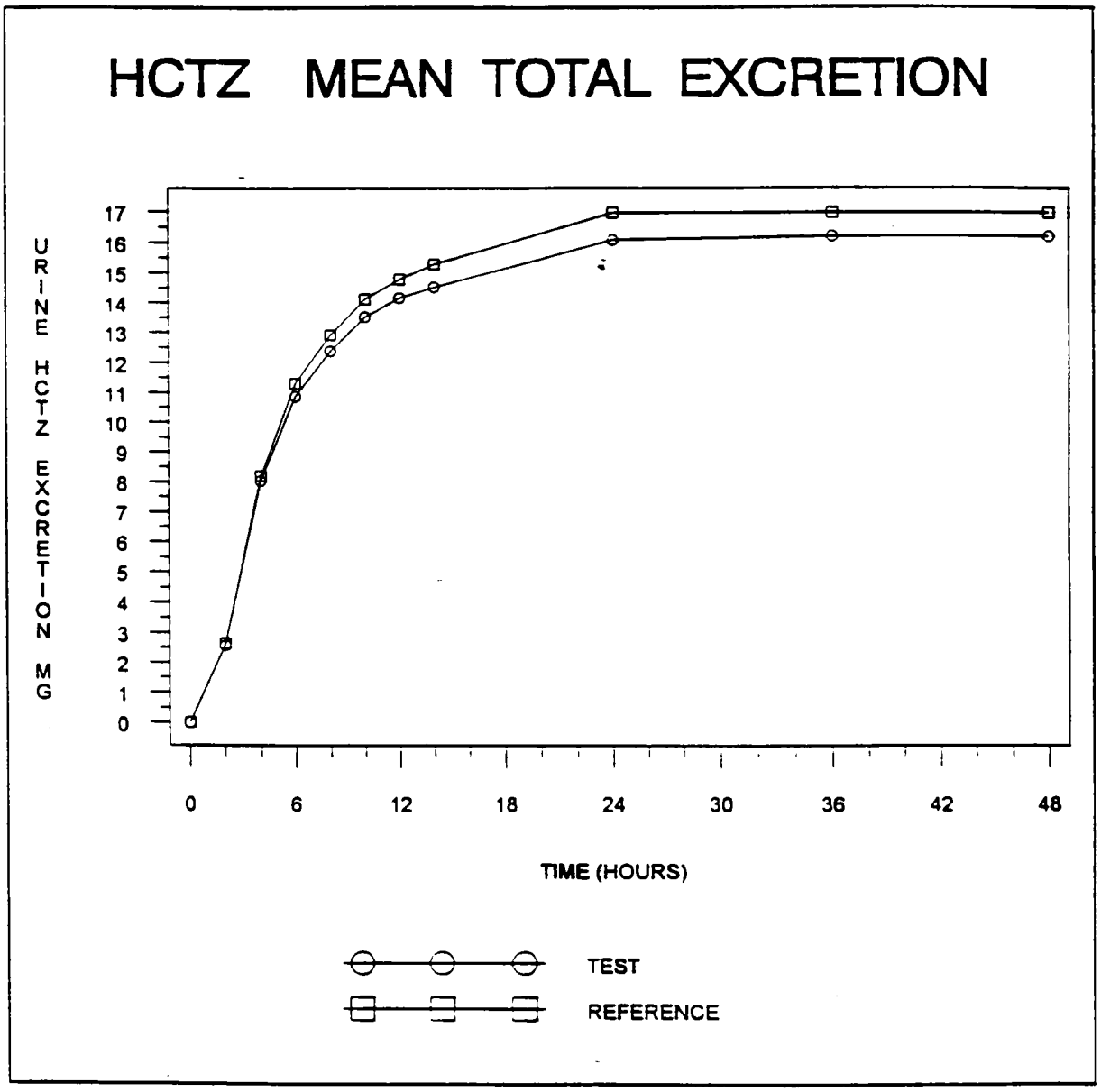
ANDA # 74-821

Figure #5 Mean Excretion Rate of Hydrochlorothiazide vs Time



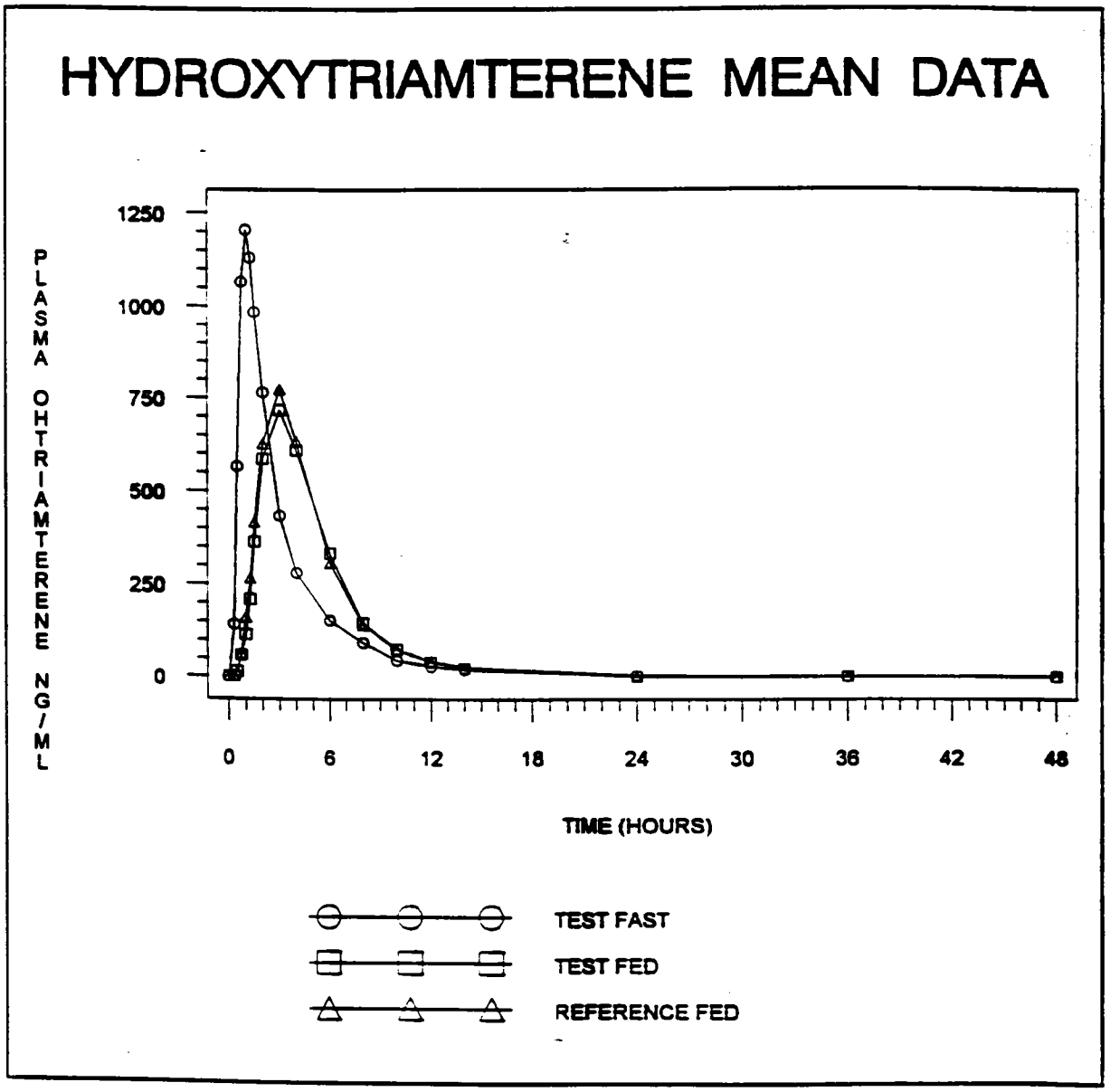
ANDA # 74-821

Figure #6 Mean Cumulative Urinary Excretion of Hydrochlorothiazide *vs* Time



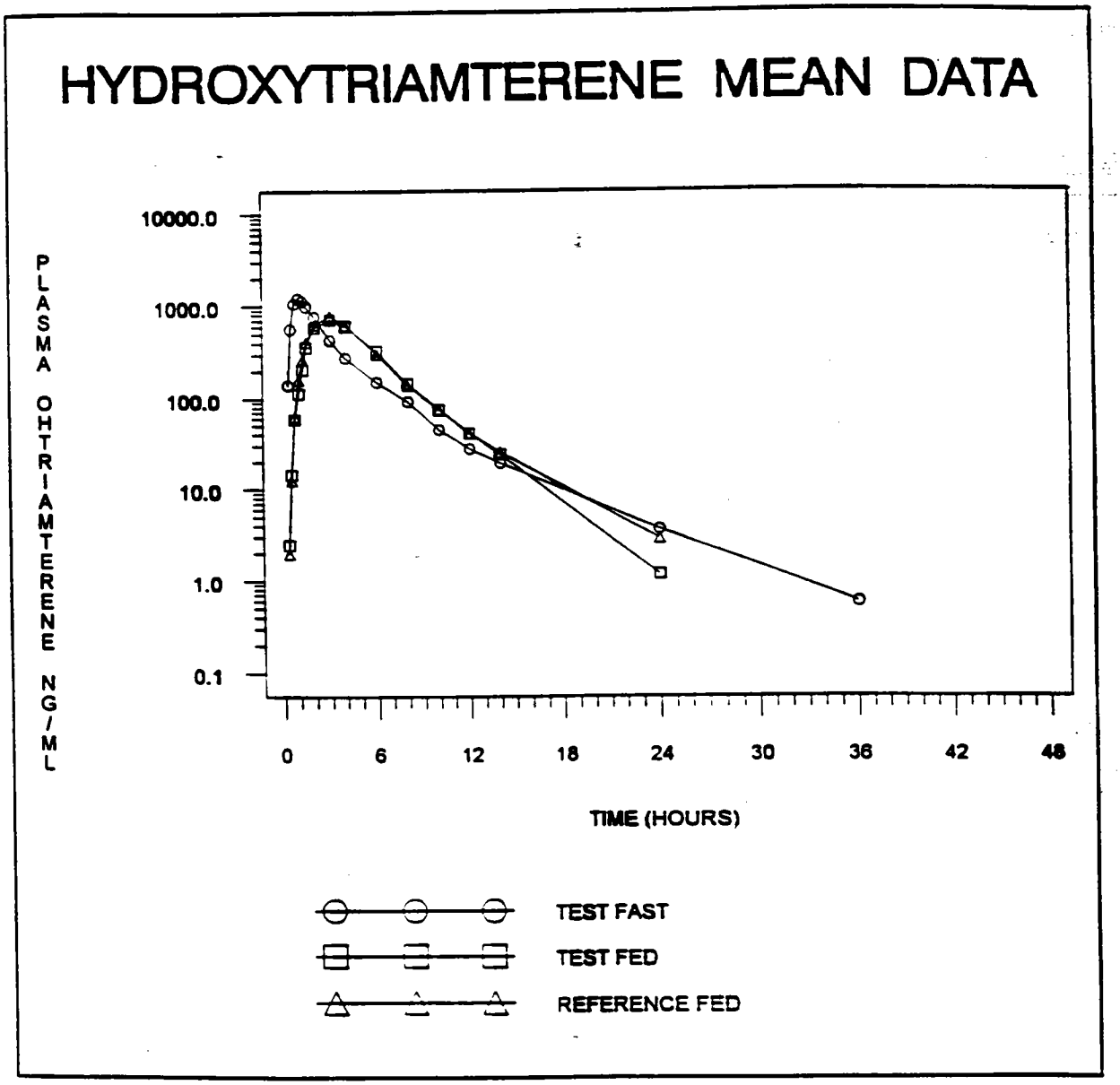
ANDA #74-821

Figure #7 Linear Plot of Mean Plasma Hydroxytriamterene Concentrations *vs* Time



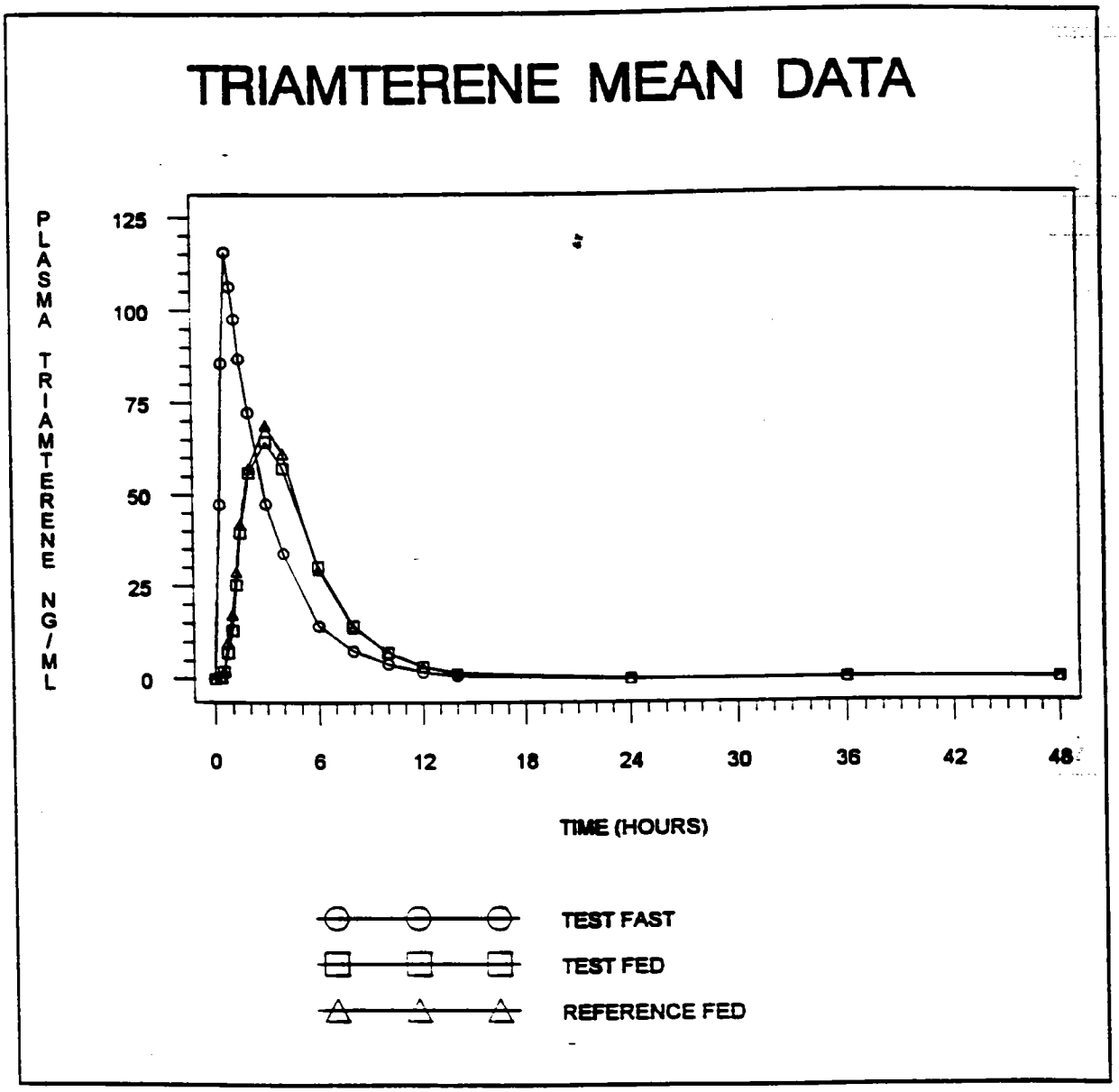
ANDA # 74-821

Figure #8 Semi-logarithmic Plot of Mean Plasma Hydroxytriamterene Concentrations vs Time



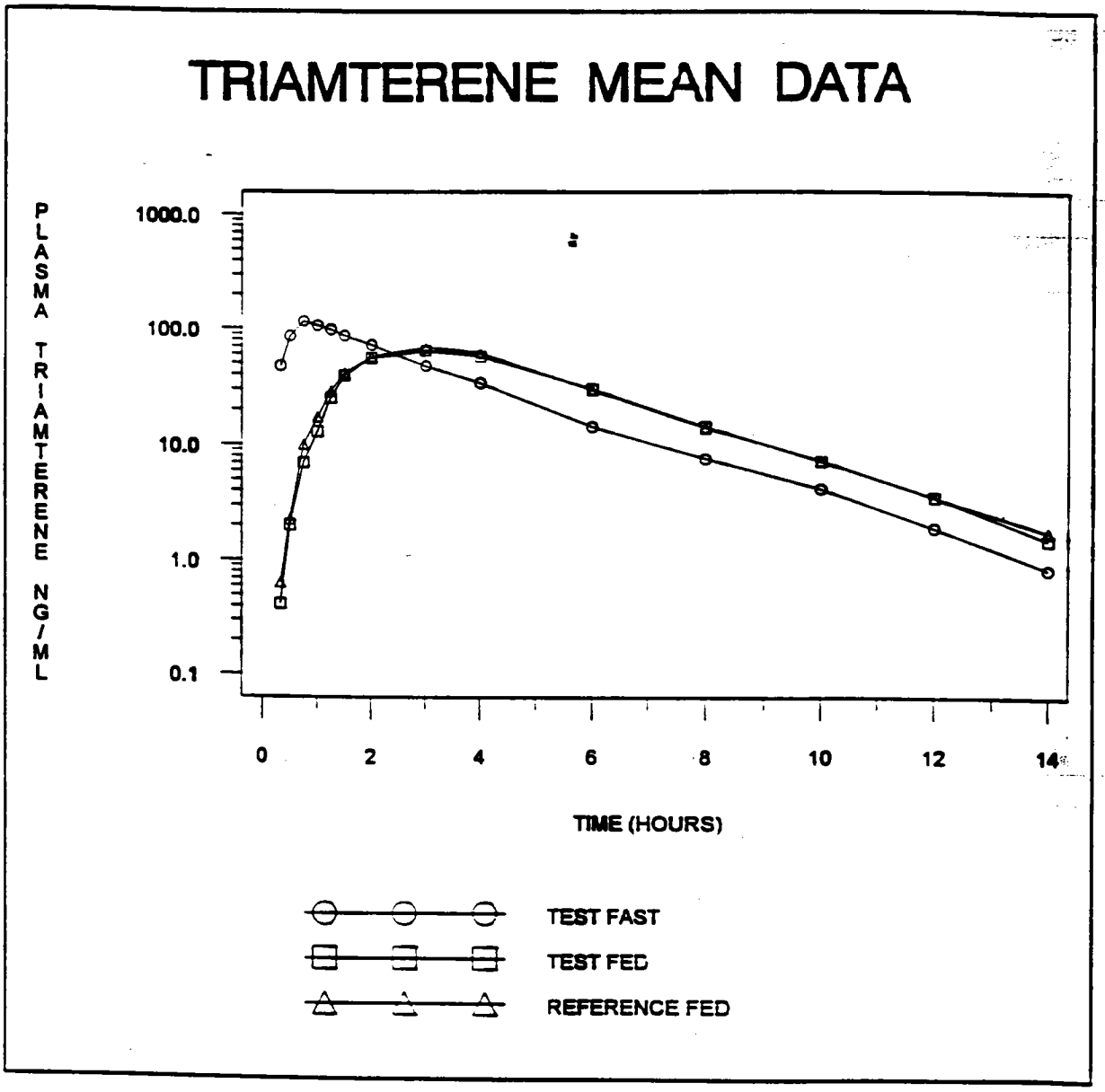
ANDA #74-821

Figure #9 Linear Plot of Mean Plasma Triamterene Concentrations vs Time



ANDA#74-821

Figure #10 Semi-logarithmic Plot of Mean Plasma Triamterene Concentrations *vs* Time



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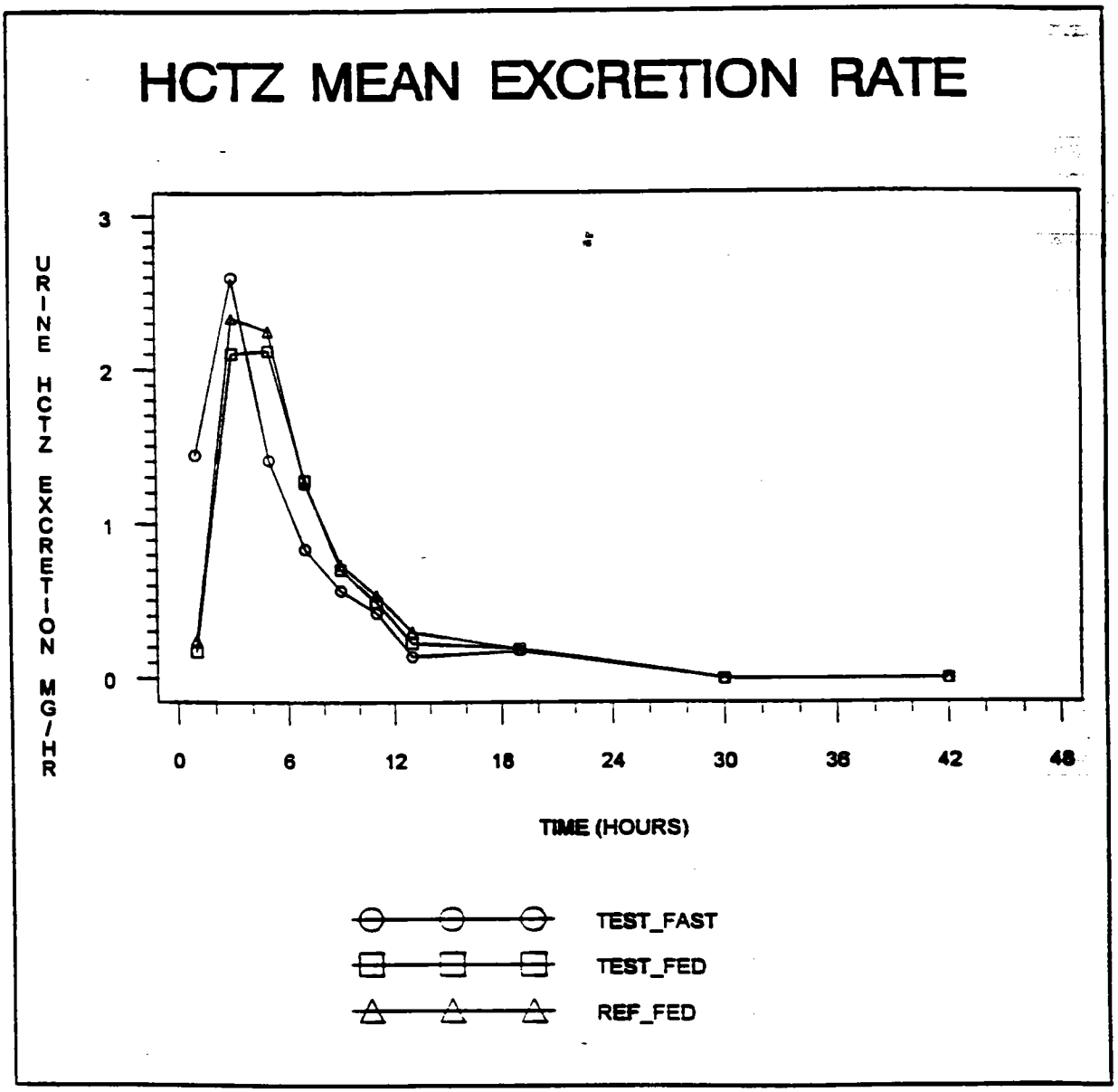
GENEVA B-01275

ANDA # 74-821

Figure # 11 Mean Excretion Rate of Hydrochlorothiazide vs Time



ANDA#74-821

Figure #12 Mean Cumulative Urinary Excretion of Hydrochlorothiazide *vs* Time